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CALCIUM AND PHOSPHORUS AND

SMITH,[1] describing the medical treatment of 314 cases of bronchial asthma writes: "When a patient was found to be sensitive, the need for general treatment was explained in detail. The general health of the subject was considered, and he was usually put on a regimen of proper rest and dietary measures, with cod liver oil and calcium lactate in moderate doses."

Novak and Hollander[2] in their study of the serum calcium of 87 patients with hay fever, hyperesthetic rhinitis and the asthmas state that the ionic calcium content of the blood serum is invariably low in hyperesthetic rhinitis and that there are also certain cases of hay fever and asthma which show a low calcium content. Calcium compounds and thyroid extract afforded temporary relief but when combined with vitamin D therapy in the form of ultra-violet irradiation it appeared to have a permanent influence on all of the rhinitis cases and upon approximately 50 per cent of those in the latter two groups.

Sterling[3] writes: "Calcium is beneficial in most hypersensitive cases whether they show a low blood calcium or not. Both calcium and phosphorus help to control the hyperexcitability of the nervous system. . . . While we cannot draw positive conclusions from a study of the above cases, calcium and phosphorus are found of great benefit in the treatment of allergic diseases. This mineral deficiency in asthmatics, hay fever, and allied diseases, whether sensitivity can be proved or not, may be the missing link which makes the allergic differ from the normal. The addition of calcium, phosphorus, and other minerals, for instance, iron, sodium and potassium salts, are possibly responsible for the favorable results in this series of cases."

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Burgess[4] is of the belief that cases of urticaria, especially those showing marked dermographism, and eczema in the vast majority of instances present a marked diminution of precipitable serum calcium. He reports that cases of urticaria and eczema were considerably improved by measures to raise the serum calcium.

Kitsuta[5] reports that in his own case he used cod liver oil and yeast for the treatment of hay fever, with beneficial results. He states: "In administering cod liver oil for the cure of hay fever already developed, I think it advisable to take about 4 teaspoonfuls three times daily. . . ."

Jones[6] found 60 per cent of his cases of exudative diathesis improved with calcium medication and parathyroid extract.

Mollison[7] states that 37 per cent of 40 cases of vasomotor rhinitis were cured and 27 per cent improved by calcium compounds and measures to increase calcium absorption.

Von Gordon[8] believes that hay fever and asthma are neuroses based upon a functional disturbance of the vegetative nervous system leading to a sympathetic hypotonia with or without vagotonia, and to a labile equilibrium of the vagus sympathetic nerves which react pathologically to normally inadequate stimuli. He contends also that a decrease in the blood calcium is one of the most important causes of this lability.

Colomb[9] states that from a therapeutic standpoint calcium is valuable for conditions associated with anaphylactic phenomena. He adds, its absorption is regulated by vitamin D.

Hutton[10] states that disturbances of calcium metabolism are likely to be present in urticaria and eczema.

Pottenger[11] thinks that calcium is definitely identified with sympathetic action. He was successful in completely relieving the paroxysms of asthma by means of calcium therapy.

Klare[12] believes that there is a relationship between the exudative diathesis of childhood and calcium deficiency. He therefore finds calcium therapy indicated in recurrent catarrh, bronchial asthma, hay fever, adenopathies and increased susceptibility to acute infections. He believes that calcium has a specific action in decreasing the hyperirritability of the autonomic nervous system.

Downing and Blumenfeld[13] report several cases of acute and chronic urticaria in which calcium therapy was effective.

Schmidt[14] found ultra-violet light of value in his own case and attributed the result partly to the antispasmodic effect of the treatment.

Ochsenius[15] points out that calcium (*Cont'd*)

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The Journal of Allergy

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Original Articles

STUDIES ON POLLEN AND POLLEN EXTRACTS

X. ANTIGENIC DIFFERENCES BETWEEN SHORT AND GIANT RAGWEED POLLENS*

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NORTH CHICAGO, ILL.

INTRODUCTION

IN RECENT years much attention has been given to the analysis of pollens and pollen extracts to determine the constituents active in hay fever and their immunologic relationships. The most thoroughly studied of these pollens are, of course, the grasses and ragweeds which constitute the most important groups with reference to hay fever. Although the close antigenic similarity among the active substances of the different pollens of a group is obvious, the antigenic identity of these substances and the possibility of using them interchangeably in the treatment of hay fever victims are still open to question.

Stull, Cooke, and Barnard,[1] using the serums of eleven grass-sensitive patients in passive transfer experiments came to the conclusion that the active principle inciting hay fever was identical in the grasses: timothy, Bermuda, Johnson, orchard, June, redtop, and rye. The serums completely absorbed with the extract of one of these species of grass pollen failed completely to sensitize the skin of a normal human being to any of them. Their extracts were prepared from dry ether-defatted pollen and standardized on the nitrogen basis.

Similarly, Stull, Cooke and Chobot,[2] by desensitization of passive transfer sites came to the conclusion that the active constituents of short and giant ragweeds are identical. The serums of nine patients were used with purified albuminous material from the pollen extracts. In addition, they were able to inject extracts of short and giant rag-

*From the Research Department of Abbott Laboratories, North Chicago, Ill.

weed interchangeably without disturbing symptoms into patients who had been built up to maximal dosage with the extract of one or the other of these pollens.

Very recently Freeman, in England,[3] reported convincing clinical evidence of the identity of the allergically active constituents of the grass pollens. He summarized evidence from two years of successful treatment of all grass-sensitive patients with the extract of timothy pollen, with concurrent skin desensitization to all grass pollens.

Other published observations which also point toward a very close similarity or identity of hay fever producing constituents within the grasses and between the short and giant ragweed are those of Spain and Hopkins,[4] Cooke and Vander Veer,[5] Walzer and Grove,[6] Scheppegrell,[7] and Brown.[8]

On the other hand, some published observations can be interpreted only as evidence against the identity of atopens in different pollens. Of 40 human cases reported by Rappaport and Johnson,[9] 20 were sensitive by skin test to short ragweed only with the reaction distinctly limited to what they term the globulin fraction. The other 20 were sensitive to both short and giant varieties with the sensitivity extending to include the albumins as well. Their high percentage of reactors to one pollen only is not in agreement with those of other investigators and is much more striking than those in their later publication.[10] In this they reported 36 patients tested with whole pollen extracts, only one of whom reacted to short ragweed only. The other 35 reacted equally well, by the dilution method, to both. By precipitin tests with serums of rabbits immunized with purified proteins of giant and short ragweed they were not able to distinguish between the proteins of these two pollens, nor the whole pollen extracts of rough marsh elder, southern ragweed, cocklebur, slender ragweed, and western ragweed.

Coca and Grove,[11] by passive transfer with two ragweed sensitive serums and subsequent desensitization, could find no difference between short and giant ragweed, but with the serum from one grass-sensitive patient they detected a difference between the pollens of timothy and orchard grass.

Bernton[12] concluded that the atopens of short and giant ragweed are not identical, basing his judgment on dates of onset and termination of symptoms and clinical effects of treatment of 89 patients. He also found among 65 of these patients cutaneously tested with serial dilutions of pollen extracts, 16 more sensitive to the giant, 45 more sensitive to the short, and 4 equally sensitive to both types. These relations in skin sensitiveness, however, did not always parallel the clinical evidence as to which species was the worse offender.

Watson and Kibler,[13] in Arizona, state that most of the grass hay fever in that territory is caused by Bermuda grass and that few of such patients give a positive skin test to timothy, although positive to the former. They report also that there were several patients who reacted to slender ragweed and who gave no reaction at all to the common ragweed.

EXPERIMENTAL

The following experimental work was begun in the hope of determining whether or not any antigenic differences could be determined between the pollens of short and giant ragweeds by the method of animal sensitization. It was thought that intensive treatment of the animals by parenteral injections would lead to more complete response than would occur in human beings from natural contact and would,

TABLE I

TRYPAN BLUE SKIN REACTIONS IN RABBITS TESTED WITH SERIAL DILUTIONS OF SHORT AND GIANT RAGWEED POLLEN EXTRACTS

RABBIT NO.	IMMUNIZED WITH	HIGHEST SKIN-REACTING DILUTIONS OF POLLEN EXTRACTS					
		9/1/32		9/27/32		10/11/32	
		SHORT	GIANT	SHORT	GIANT	SHORT	GIANT
1	Giant	*	*	0	1,000	0	0
15	Giant	16,000	64,000	64,000	256,000	1,000	4,000
17	Giant	16,000	64,000	1,000	4,000	1,000	4,000
32	Giant	4,000	16,000	256,000	256,000	16,000	1,024,000
60	Giant	*	*	1,024,000	4,096,000	*	*
8	Short	*	*	256,000	256,000	16,000	256,000
23	Short	16,000	1,000	64,000	4,000	4,096,000	16,000
46	Short	16,000	4,000	*	*	*	*
68	Short	16,000	1,000	4,000	0	4,000	4,000
595	Short	64,000	16,000	4,000	4,000	16,000	1,000

*Diffuse blue; no reading made.
0 = No reaction with 1:1000, the lowest dilution tested.

therefore, have greater possibility of revealing any antigenic difference that might be present.

Rabbit Skin Tests.—Rabbits were immunized by intraperitoneal injections of whole pollen suspensions, some with giant and some with short ragweed, and their skin reactions tested with serial dilutions of the whole pollen extracts by the trypan blue method previously reported by us.[14] Whole pollen was used for immunization because in our experience it stimulated the development of skin sensitiveness much better than the extracts. After a few injections the animals were tested by injection of the trypan blue solution intravenously, followed immediately by injections of serial dilutions of extracts of the two pollens into the skin of the abdomen. A positive reaction was indicated by the accumulation of the dye, giving a blue color at the site of the intradermal injection.

Ten rabbits were immunized, each with five intraperitoneal injections of 3.0 c.c. of a 1 per cent pollen suspension; five animals with short ragweed, and five with giant, over a period of fourteen days. Ten days after the last injection they were skin tested with serial dilutions of the pollen extracts. The extracts were prepared by shaking one gram of dry pollen in 100 c.c. of water containing cresol 0.1 per cent and dextrose 5 per cent, and filtering after a few hours. This was called a 1:100 extract and served as the basis for making further serial dilutions in the same menstruum. After the first and second tests, the animals were allowed to rest twenty-six days and fourteen days respectively before the next test was made; they were given one intraperitoneal injection of whole pollen during the first interval.*

An examination of Table I reveals a very definite specificity in the skin reactions of the rabbits to the pollen extracts. In general, those immunized with giant ragweed react with higher dilutions of giant than with short, and vice versa. Of the fifteen tests made on the five giant ragweed animals, ten showed reaction to higher dilution of giant ragweed pollen extract than of short, one showed equal reaction to both, one showed reaction to neither, and three were not readable because of a diffuse blueness of the skin, masking the local reaction. Of the fifteen tests made on the five short ragweed animals, eight showed reaction to higher dilution of the short ragweed pollen extract than of the giant, three showed equal reaction to both, one reacted to a higher dilution of giant, while three were not readable. In the first tests all the animals reacted to higher dilutions of the homologous than of the heterologous pollen extract. The failures of such specific reactions are seen only in the second and third tests after each animal had experienced intradermal injections of both pollens.

It might be mentioned here that the third tests on the animals were read by one who was ignorant of the order in which the intradermal inoculations were placed. The extracts were identified by number and after all the readings were made this observer was able to identify the two solutions by examining the test protocols.

Precipitin Reactions.—The day before the third skin test each animal was bled 5 c.c. to 10 c.c. from the marginal ear vein and the serum tested for the presence of precipitin against 1:200 dilutions of pollen extracts. These were made by diluting the 1:100 solutions in dextrose-cresol menstruum with equal volumes of salt solution. The tests were made in short 5 mm. tubes by carefully overlaying the serum with the pollen extract, using a capillary pipette. In tubes of this size only a very small amount of material was necessary and sharp

*We are indebted to Miss Constance Seeber for much technical assistance in immunizing the animals and in making the skin tests.

contacts between the serum and antigen were maintained for almost two hours. During this time they were watched closely and records kept not only of the comparative heaviness of the white ring of pre-

TABLE II

PRECIPITIN TESTS WITH SERUMS OF RABBITS IMMUNIZED WITH SHORT AND GIANT RAGWEED

RABBIT NO.	IMMUNIZED WITH	PRECIPITIN TESTS WITH EXTRACTS OF			
		SHORT	GIANT	TIMOTHY	ORCHARD GRASS
8	Short Ragweed	tr.	0	0	0
23	Short Ragweed	+	0	0	0
46	Short Ragweed	+	0	0	0
68	Short Ragweed	0	0	0	0
595	Short Ragweed	+	tr.	0	0
1	Giant Ragweed	+	+	0	0
15	Giant Ragweed	tr.	+	0	0
17	Giant Ragweed	tr.	+	0	0
32	Giant Ragweed	0	0	0	0
60	Giant Ragweed	+	++	0	0

cipitate but also the time necessary for its formation. All of these readings were checked by a disinterested observer, who did not know the significance of his readings and could not have been biased.

In Table II, where these results are recorded, the specificity of the pollens in their reactions to precipitin is apparent. Of the five serums of the short ragweed treated rabbits, one was negative to both extracts, three precipitated with short ragweed pollen only, and one gave a much less marked reaction with giant than with short. Of the five giant ragweed treated rabbits, one serum showed precipitin reactions of equal intensity with both species, three gave weaker reaction with short than with giant, while one reacted with neither. None of the reactions was very strong, even the best ones requiring five to ten minutes for development. The difference in rate of the reactions, which are not included in the table, were consistent with the intensity as recorded in the final reading.

COMMENT

The recorded results of the animal skin tests and of the precipitin tests with their serums represent, we believe, unbiased observations. Unless there is some loophole in the experiments which we have failed to consider, they lend considerable support to the conception of the antigenic individuality of the pollens of the giant and short ragweeds. While cross reactions were obtained, demonstrating the group relationship of the two species, yet their difference is obvious in the more pronounced reactions to the homologous pollen extracts in both the rabbit skin tests and the precipitin tests.

Three possible assumptions might be made to explain these results: (a) that the two pollens contain certain antigens in common and others that are distinctly different and peculiar to the individual species; (b) that the two pollens may contain the same antigenic constituents but in different proportions; and (c) that instead of any of the antigens of one pollen being identical with any of those of the other, certain of them may be so similar in chemical structure as to give cross reactions. Our experiments throw no light on these questions but they demonstrate with certainty that the antigenic make-up of the giant ragweed pollen is different somewhat from that of the short ragweed pollen.

These results may or may not be applicable to human hay fever. We will admit that some of the ragweed hay fever patients in a given locality may be treated just as successfully with one pollen as with the other. The possibility is obvious, however, that antigenic differences between the two, demonstrable in artificial sensitization of the lower animals, may on occasion be revealed in the natural sensitization of human beings. We[15] have previously reported passive transfer experiments with one serum in which the sites desensitized with giant ragweed still were found reactive to a mixed ragweed pollen extract. Recently, through the courtesy of Major A. Parker Hitchens at Fort Sheridan, Illinois, a case of marked skin sensitiveness to short ragweed with no reaction to giant has come under our observation. Passive transfer and absorption tests with the serum from this patient were in agreement with his skin tests.

CONCLUSIONS

1. The trypan blue skin reactions in rabbits sensitized, some by injections of short ragweed pollen and others by injections of giant ragweed pollen, showed a greater skin sensitiveness of the animals to the homologous than to the heterologous pollen extract.

2. Precipitin reactions with serums from these same animals also demonstrated the same specificity.

3. From these results, the antigenic structure of the short ragweed pollen is concluded to be different from that of the giant ragweed pollen.

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ON THE PLAN OF STANDARDIZATION OF POLLEN EXTRACTS PROPOSED BY COOKE AND STULL*†

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BY STANDARDIZATION of a pollen extract is meant the quantitative estimation of its relative, specific activity in the pollen-sensitive person. This relative activity can be estimated directly by means of intracutaneous tests with different dilutions of the extract in pollen-sensitive persons. There are also two indirect methods that have been used to estimate the relative strength of pollen extracts. The first of these was that of Noon who used a certain weight of timothy pollen per volume of extracting fluid; the second was that of Cooke, who standardized the extracts according to their total nitrogen content per cubic centimeter.

PROTOCOL FROM REPORT BY COLONEL S. W. FRENCH OF THE CLASSIFICATION OF HAY FEVER SUBJECTS WITH RESPECT TO THE DEGREE OF THEIR SENSITIVITY

CLASSIFICATION AS TO SENSITIVITY	TIMOTHY GRASS	RAGWEED GIANT AND SHORT COMBINED	CARELESS WEED	MT. CEDAR
"A" Skin positive to an extract of 0.0001 N per c.c.	2– 2.7%	3– 3.1%	0– 0.0%	5–21.0%
"B" 0.001 N per c.c.	6– 8.0%	7– 7.3%	3– 5.3%	4–20.0%
"C" 0.01 N per c.c.	10–13.3%	15–15.6%	10–17.5%	1– 5.2%
"D" 0.1 N per c.c.*	45–60.0%	49–51.0%	32–56.2%	10–52.8%

*The 0.1 solution of the timothy pollen extract represented a 1 per cent extract (by weight); the 0.1 solution of the mountain cedar pollen extract represented a 7 per cent extract (by weight).

The method of Noon, while it is satisfactory for extracts of timothy pollen cannot be uniformly applied with all pollens. Colonel S. W. French[1] has found that compared with timothy pollen extracts prepared on the basis of an equal weight of pollen per volume of extract, mountain cedar pollen extracts are much weaker than the timothy pollen extracts. However, when the two extracts were compared in strengths of equal total nitrogen concentration, they exhibited apparently equal specific activity (in skin tests).

*From the New York Postgraduate Medical School of Columbia University and Lederle Laboratories.

†Read before the Society for Study of Asthma and Allied Conditions at Washington, May 6, 1933.

It is seen that if, as is usual with other pollen extracts, a 1 per cent extract of mountain cedar pollen had been used as the strongest intracutaneous testing solution, some of the 10 subjects who reacted only to the 7 per cent extract might have been passed as non-sensitive or might have been given inadequate dosage in treatment.

In another series of experiments[2] French was able to show that during the aqueous extraction of pollen the atopic excitant dissolves out of the pollen grains at the same rate as the whole extractable nitrogen. This he accomplished in the following manner: two successive saline extracts were made of the same specimen of pollen, the first extraction being continued for ten minutes, the second for about twenty-four hours. The nitrogen content of the two extracts was determined and the extracts were both diluted to an equal nitrogen content. When tested in the skin of pollen-sensitive subjects these two diluted extracts were found to be equal also in their specific activity; in other words, the ratio of activity to total nitrogen content was the same in the first and the second extract.

These two observations, taken together, clearly indicate the superiority of the total nitrogen content of pollen extracts over the weight of pollen per volume of extract as an indirect criterion of the activity of the extracts.

However, if a certain pollen (timothy, for example) is once standardized by Noon's weight-per-volume method, the same method applied to the same pollen gives extracts of practically equal activity *provided the pollen is always properly collected and preserved and if the extracts are always prepared in the same manner.**

These important conditions have not always been observed, and when this has happened both of the two indirect methods of standardization have failed to indicate the specific activity of the extracts.

In an apparent effort to uncover some other explanation of the irregularity in the activity of different extracts of the same kind of pollen, Cooke and Stull[3] have abandoned the standardization by total nitrogen content and propose the adoption of a unit standard calculated from what they call the "protein" content.

Their suggestion is drawn from the belief of these writers that the excitant of hay fever in pollen is the protein, as quantitatively deter-

*As this paper was being sent to press a copy was submitted to Dr. S. W. French, who has made the following interesting comment: "There is one paragraph with which I am not ready to agree with you, for the following reason: A year or so ago I obtained some timothy pollen from California and some timothy pollen from Virginia. We made some extracts with each of these pollens using identical technic in both cases; in fact, the two extracts were prepared at the same time. Upon doing a Kjeldahl nitrogen determination on both of these extracts we found that the extract made from the California grown timothy pollen was about 40 per cent stronger in nitrogen than that of the Virginia grown pollen. For this reason I believe that the soil, climate, moisture, and possibly the time of year at which the pollen is grown, have a great bearing on the amount of nitrogen in the pollen. Of course, I do not contend that this one comparison is conclusive, but it leads me to believe that a nitrogen determination should be done in all pollen extractions, to the exclusion of the weight-per-volume method."

mined by its phosphotungstic acid precipitation out of the saline extracts. Hence, we shall first examine the validity of this assumption.

In the first attempted study of the nature of the pollen excitant Grove and Coca[4] found no loss of activity in an extract which had been treated with trypsin and freed of detectable nitrogen (as compared with the control) by dialysis through a collodion sac.

These authors concluded, therefore, that the pollen excitant is not the easily digestible and dialyzable protein and it was classed by them with the ferments as active substances out of reach of the present technical methods of chemical analysis. However, they concluded that the pollen atopen is not the proteolytic ferment of the pollen and postulated no ferment nature for the atopen.

These experiments could not exclude the possibility that the pollen atopen possesses a protein nature, especially since they demonstrated its relative nondialyzability.

Most of the later chemical studies of the pollen atopen have consisted either in attempts at the separation of an active "protein" constituent or in attempts to destroy the activity of the extracts in the course of proteolytic digestion.

As to the first category of these studies it should be recalled that other chemically indefinable substances of specific activity, such as ferments and antibodies, regularly follow the proteins of their natural medium when these are precipitated out of solution by salting or otherwise. The results of the digestion experiments ought to be accepted with some reservation. If the pollen extract is inactivated in the course of proteolytic digestion, this hardly proves that the atopen is a protein. It is conceivable that after the atopen has been freed completely of the associated possibly protective protein, it may then be exposed to the destructive action of the acid property of the digestive fluid (in peptic digestion) or to the adsorptive property of some component of the digestant solution.

A closely analogous situation is presented in the digestion experiments all of which, in a number of different experienced hands, yielded results that indicated a protein nature of a component of alexin (complement). Alexin seemed to be a digestible protein. Finally, however, E. F. Grove[5] was able to demonstrate that the supposed digestion of alexin was nothing but an inhibition phenomenon as shown by the existence of a prezone of lacking inhibition when larger quantities of the digestive fluid were mixed with the complementary serum.

The experiments reported by Grove and Coca were so consistently clear-cut, as far as the present question is concerned, that they were not repeated in this study. However, in view of the use, by Cooke and Stull, of the phosphotungstic acid-precipitable fraction of pollen

extracts as their basis of standardization this fraction has been studied by the method of dialysis as a means wherewith one may judge of its general chemical nature.

There are early observations indicating that native protein may pass slowly through a certain type of semipermeable membrane, but it has recently been found that native proteins are actually dialyzable through parchment, collodion membrane, or animal membrane. However, the rate of dialysis is so slow (about 1 per cent in six days, according to Coca[6]) that it still stands as a reliable criterion of the typical native protein molecule.

If, then, the phosphotungstic acid-precipitable substance in pollen extracts is, save for "traces of inactive protein (probably globulin)" an albumin, simple dialysis for the period of six days should result in a negligible loss of the phosphotungstic acid-precipitable fraction. Cooke and Stull[3] write: "Also the whole extracts of timothy and ragweed pollen after dialysis in a hardened membrane against distilled water contained nondialyzable active protein nitrogen of the same magnitude as determined by phosphotungstic acid precipitation." Overlooking the obscurity of the expression "hardened membrane" and also the omission in the authors' statement of the length of time during which the "dialysis" was continued, one could obtain the impression from the quoted passage that the phosphotungstic acid-precipitable nitrogen represented nondialyzable native protein.

We have been unable to confirm this. In a number of consistent experiments we have seen such a rapid dialysis of phosphotungstic acid-precipitable nitrogen as to make it certain that *by far the greatest part of it is not native protein.*

The collodion sacs used in the present study were made with the method described in the cited paper of Grove and Coca. Five successive coats of the collodion solution (one ounce of the dry chips in 600 c.c. of absolute alcohol and water-free ether) were applied, resulting in a thick walled sac. No trace of leakage could be detected when the sac was filled with 95 per cent alcohol nor when it was subjected to a pressure of 30 inches of water.

A freshly made collodion sac possesses a decided property of adsorption which, as will be presently seen, lends itself advantageously to the object of this investigation. This property of adsorption can be largely exhausted by a brief treatment of the sac with 10 per cent peptone followed by immersion of the sac in changes of water or saline solution over a period of twelve days. The last wash water contained 0.016 milligrams of nitrogen per cubic centimeter.

When a ragweed pollen extract containing 0.784 mg. of total nitrogen per cubic centimeter (30.7 per cent precipitable with phosphotungstic acid) was dialyzed against the bicarbonate saline solution (Coca[7]) at 7° C. in a peptone treated collodion sac, the outside fluid being changed two or three times daily, the total N per cubic centimeter on the seventh day was found to be 0.0794 milligrams or a little over one-tenth of the

original. The activity of this dialyzed extract in sensitive skins at this time was practically identical with that of the original extract. On the thirteenth day the total nitrogen content of the dialyzed extract had fallen to 0.047 mg. per cubic centimeter and further dialysis brought this figure down to 0.027 on the nineteenth day—a total loss of 96.6 per cent, of which 28.26 per cent was precipitable with phosphotungstic acid (that is 94 per cent of the phosphotungstic acid-precipitable nitrogen).

A nitrogenous substance which dialyzes at the rate of over 90 per cent in six days cannot be classified as albumin, but must possess a smaller molecular size. It may be recalled here that even polypeptids are precipitable with phosphotungstic acid. A solution of leucyl-glycyl-glycine which was given us by Dr. Karl Landsteiner was instantly precipitable with this reagent, the milky cloud of the first precipitation later settling in transparent crystals.

The foregoing experiment contributes illuminating confirmation of the earlier observations of Grove and Coca. It indicates the possibility that the tryptic digestion, which was used as an aid to elimination of "protein" in the pollen extracts, was needed for only a very small fraction of the nitrogenous substances of the extracts.

When it was seen how quickly the greater part of the P-T-Å-precipitable nitrogen diffuses through the sac wall, it seemed possible that this circumstance could be utilized to obtain that substance freed from the pollen atopen by dialyzing it through a new untreated sac possessing the property of adsorption mentioned above. This proved to be the case, as is shown in Table I.

TABLE I

GIANT RAGWEED POLLEN EXTRACT (70 C.C.) DIALYZED THREE DAYS IN NEW COLLODION SAC WITHOUT CHANGING OUTSIDE FLUID (80 C.C.)

	TOTAL N PER C.C. MG.	PRECIPITABLE N PER CENT		SKIN TESTS IN HAY FEVER SUBJECTS‡							
				1 BC	2 B	3 C	4 C	5 C	6 C	7 D	8 B§
Original extract	0.784	30.7	0.0003*	+±	+±						+±
			0.001	++±					+±		
			0.003			+±	+±	++±		±	
Dialyzed	0.320	30.6	1-2613†	++	±						+
			1-784	++					+		
			1-261.3			+±	+±	+±		±	
Dialysate	0.290	21.5	0.29*	*Negative* in one Class B and two Class BC subjects							

*Milligrams of N per cubic centimeter.

†Dilution by volume.

‡By Katherine L. Bowman.

§The use of letters in this classification is interpreted in column 1 of Colonel French's protocol on page 354. The intracutaneous test is used and the "positive" reaction is a wheal with definite pseudopods.

The data in the table show that when the pollen extract had been dialyzed three days in the new collodion sac and was compared with

the original extract in identical dilutions by volume, it was seen to have lost slightly but perceptibly some of its activity—probably by adsorption on to the new sac. It is noteworthy that although over half of the total N per cubic centimeter had been lost in the process, the percentage content of P-T-A-precipitable N was actually diminished instead of greatly increased, as should have been the case if this fraction were less rapidly dialyzable than the nonprecipitable fraction.

The outstanding feature of the table is the finding in the examination of the dialysate. The dialysate contained a smaller percentage of P-T-A-precipitable N (21.5) than the dialyzed extract (30.6), the difference being necessarily due to adsorption on the part of the sac wall. This also accounts for a large part of the difference between the total nitrogen content of the dialyzed extract and that of the dialysate. When a peptone-treated sac is used, the total N content per cubic centimeter becomes nearly the same both outside and inside the sac in three days.

When the dialysate (containing 0.29 mg. of total N per cubic centimeter and 21.5 per cent of the P-T-A-precipitable N) was tested without dilution by intracutaneous injection in hay fever subjects, it was found to be *free from the pollen atopen.* This experiment was a repetition of a similar one with another new collodion sac in which the finding was the same. The result of it is thus the opposite of those of Grove and Coca and entirely consistent with them.

In the latter, the *pollen atopen was freed from pollen nitrogenous substances,* whereas in the former P-T-A-precipitable N has been obtained by dialysis free from the pollen atopen.

The two series of experiments individually and taken together nullify the assumption of Cooke and Stull that the P-T-A-precipitable substance of pollen extracts is the excitant of hay fever and therefore must be taken as the basis of chemical standardization of pollen extracts.

Cooke and Stull report the absence of alcohol-precipitable substance in an extract of cat-tail pollen and use this finding to explain why this pollen does not act as an excitant of hay fever. In the present study, extracts of two different samples of cat-tail pollen have been examined and both were found to contain a considerable quantity of P-T-A-precipitable N—29.26 and 41.34 per cent respectively.

It is a noteworthy fact that in the paper by Cooke and Stull, although they report large differences in the percentage "protein" content of different extracts of the same kind of pollen (for example 24 per cent in the timothy pollen of 1921 as compared with 54 per cent in the timothy pollen of 1931), yet they offer no comparison of the two extracts as to specific activity through quantitative skin tests in pollen-sensitive persons. Instead of such a direct approach to this essential question on which their whole thesis rests, these authors content themselves with the following statements:

"When such extracts were diluted on a protein nitrogen basis, they compared favorably in activity. Furthermore, on this protein basis, one-year-old and new extracts have been given interchangeably in therapeutic doses without constitutional reactions."

The total nitrogen content of pollen extracts has been found to be a practically reliable guide in their standardization, and when an extract standardized by total nitrogen content has been found to be relatively weak, this could generally be shown to be due to improper technic in the collection and preservation of the pollen or in the preparation of the extract.

TABLE II

RESULTS OF COMPARATIVE SKIN TESTS IN HAY FEVER SUBJECTS WITH TIMOTHY POLLEN EXTRACTS CONTAINING DIFFERENT PROPORTIONS OF PROTEIN NITROGEN*

(T 1922 = 52.27% Precipitable N; T 1932 = 52.2% Precipitable N; T 1931 = 36.84% Precipitable N)

PATIENT	CLASS	TOTAL N MG. PER C.C.	REACTIONS		
			T 1922	T 1931	T 1932
M. B.	CD	0.003	+	+	+
R. B.	CD	0.01	++±	++	+±
L. U.	D	0.01	++	+	+±
J. W.	D	0.1	±	+±	±
N. C.	D	0.1	++	++±	++
B. L.	D	0.01	±	+	±
R. L.	C	0.001	++	++	++
A. L.	B	0.0003	+±	+	+±
E. L.	C	0.001	++±	+±	++±
G. R.	B	0.0003	+±	+±	±
I. G.	C	0.001	+	+	+
A. R.	CD	0.01	+	+±	+

*By Katherine L. Bowman.

The fact is illustrated in the results of intracutaneous tests of three different timothy pollen extracts. (See Table II.) If one gives a numerical value to the different reactions as indicated by the symbols, it appears that the extract of the 1932 pollen is slightly weaker than either of the other two—a difference which might be due to a slight technical difference in the preparation of the extracts.

It would seem evident from the comparison of these three extracts that their specific activity is not a function of their content of phosphotungstic acid-precipitable substance, because if this were the case the extract of the 1931 pollen should have been weaker than the other two.

In order to see what difference in the comparative skin tests could be expected between extracts differing in activity in the same degree as that represented by the precipitable N content of these three pollen extracts, one of the extracts was diluted 36.8 to 52.2 and this solution was compared with the original in nine hay fever subjects in the various subdilutions indicated in Table III.

TABLE III

RESULTS OF COMPARATIVE SKIN TESTS IN HAY FEVER SUBJECTS WITH TIMOTHY POLLEN EXTRACTS HAVING RELATIVE STRENGTHS RELATED TO EACH OTHER AS 52.27 (A) IS TO 36.84 (B)*

PATIENT	CLASS	A		B	
		N PER C.C. MG.	REACTION	N PER C.C. MG.	REACTION
S. B.	C	0.001	++	0.0007	+
J. F.	C	0.003	++±	0.0021	+±
L. L.	B	0.001	+++	0.0007	++
I. C.	C	0.001	+±	0.0007	+
E. L.	AB	0.0003	+++	0.00021	+±
G. R.	B	0.0003	+±	0.00021	+
I. G.	C	0.001	+±	0.0007	±
F. B.	C	0.001	++±	0.0007	+
A. L.	C	0.001	++	0.0007	+

*By Katherine L. Bowman.

It is seen that in every test of the two solutions the more dilute of the two produced decidedly weaker reactions, in fact, very close, on the average, to one-half as strong. The difference in the content of the two solutions in active substance is actually magnified in the results of the skin tests.

The results of these comparative tests indicate that if, as Cooke and Stull have assumed, the specific activity of a pollen extract is determined by its content in precipitable N, the extract of the 1931 timothy pollen (Table II) should have been about half as active in the skin tests as those of the 1932 and 1922 pollens.

One must conclude from the foregoing that the proposal of Cooke and Stull is not only based on a false assumption as to the chemical identity of the pollen excitant but it is also incorrect in its practical application.

Cooke and Stull report a loss of "protein" nitrogen in timothy pollen extract during a period of eight months of 33 per cent which corresponded with its loss in activity.

In the present study a rye grass pollen extract prepared in 1929 was compared with a fresh 1933 extract in activity and found to have lost at least 90 per cent of its original activity yet its content in precipitable N was at the usual level for grass pollens—53.3 per cent.

SUMMARY

It has been proposed by Cooke and Stull that pollen extracts be standardized according to their content of phosphotungstic acid-precipitable nitrogen. They base this proposal on the following arguments: (1) they believe that this fraction represents (for the greater part) an albumin, which they assume to be the excitant of hay fever in the pollen; (2) they claim that they were able quantitatively to separate this "protein" fraction from the nonprecipitable N by dialysis; (3) they report that a pollen extract which had lost about 33 per

cent of its original activity after eight months, had lost also 33 per cent of its "protein" N; (4) referring to the nonoccurrence of hay fever caused by cat-tail pollen, they explain this as due to the absence of alcohol-precipitable N in cat-tail pollen extracts.

All of these four arguments have been examined and found fallacious.

1. The phosphotungstic acid-precipitable substance in pollen extracts, cannot be an albumin because it is rapidly dialyzable; after it has been obtained by dialysis through a fresh collodion sac, it is found to be inert, the excitant remaining within the sac or adsorbed on the membrane.

2. As has just been indicated, the separation of the nondialyzable N and dialyzable N in pollen extracts could not be confirmed.

3. The parallelism between loss of activity and loss of precipitable N could not (in the one case studied) be confirmed.

4. The absence of alcohol-precipitable substance in cat-tail pollen, could not be confirmed.

The foregoing observations deprive the proposal of Cooke and Stull of its theoretical foundation; when practically applied to the standardization of extracts of three different timothy pollen specimens, their plan was found to produce unreliable results, whereas the standardization by total N* content was quite satisfactory.

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(For discussion, see page 445.)

*Most of the nitrogen determinations (Kjeldahl) were carried out by Mr. E. L. Milford of Lederle Laboratories.

THE EFFECT OF CONSECUTIVE YEARS OF TREATMENT UPON CUTANEOUS SENSITIVENESS IN LATE HAY FEVER*†

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IT IS generally agreed that variations from year to year in the degree of cutaneous sensitiveness in treated hay fever cases are slight, regardless of the clinical results obtained. The alleviation of symptoms is not accompanied, even temporarily, by a corresponding lessening in the skin reaction to the pollen excitants. Indeed, individuals who manifest a definitely decreasing clinical sensitiveness, lasting in character, often maintain a fairly constant level of reaction by test; and in many whose symptoms have permanently disappeared, the skin sensitiveness remains. It has been our impression, shared by many others, that, while the cutaneous reactions obtained upon test at the conclusion of a season of intensive treatment demonstrate but little change from those made at the beginning, more prolonged treatments tend to influence the skin sensitiveness.

Rackemann,[1] in 1926, described a series of 76 ragweed patients having had four or more consecutive years of treatment with ragweed pollen extracts. He limited his discussion to the clinical results attained and did not draw conclusions from his series of tracings of the yearly cutaneous reactions to tests with pollen extract dilutions, although a gradual lessening in sensitiveness would seem evident from his charts. Vander Veer[2] also has observed the gradual lessening of sensitiveness in persistently treated cases. Such diminution in the skin response is gradual, almost imperceptible.

Colmes,[3] however, describing the results of a single season of treatment upon cutaneous reactivity, contrary to the findings of the majority of investigators, concluded that at the end of the season cutaneous reactions to pollens were unaffected in only 10 per cent, were markedly reduced in 81 per cent and disappeared in 9 per cent. Even more profound effects are claimed by British workers,[4] who state that "complete obliteration" of the skin reaction is obtained in all their grass hay fever cases as a result of a single season's treatment. In our hands such marked diminution in skin sensitiveness has not occurred when the pollen extracts employed for testing at the end of the season were comparable in freshness and potency with those used in the beginning.

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†Read before the ninth annual meeting of the Society for the Study of Asthma and Allied Conditions, Washington, D. C., May 6, 1933.

Since we shared the more conservative idea that any tangible differences would be found only in cases treated and studied over periods of time longer than one year, this investigation was attempted. Cases of late hay fever, sensitive to ragweed, and treated by the prophylactic (or preseasonal) method over an uninterrupted number of years, were selected. Two groups of hay fever patients were studied; the first, consisting of 38 patients received treatments in the three years, 1930 to 1932; the second, consisting of 30 patients, received treatments in the four years, 1929 to 1932.

The testing and treatment of these patients were carried out under conditions as nearly identical as possible. The ragweed extracts were made each year according to the same formula and of pollen from the same source. The technic in testing (intracutaneous method); the method of classification of the degree of sensitiveness; the prophylactic

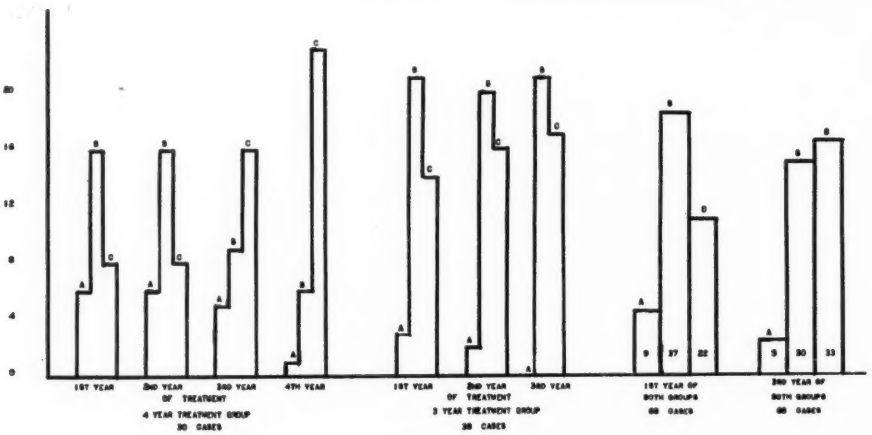

Chart 1.

treatment schedules; and, in a large measure, the personnel, were identical for the four-year period studied. At the beginning of each season, each patient was placed, according to his sensitiveness as determined by intracutaneous test, into one of three groups following our usual custom; class A, being considered quite sensitive; class B, sensitive; class C, less sensitive; this grouping being a modification of that originally described by Vander Veer, Cooke and Spain.[5]

By referring to Chart 1 it will be noted that while the total number of A cases in the two groups is small, there is a progressive diminution in their number from year to year. In the four-year group there is a gradual decrease in the number of B cases and an increase in C cases, all of the changes occurring after the second year. The relative changes in the B and C cases are most marked in the fourth year. In the three-year group similar changes occur, beginning with the second year. A composite graph of the first year of both groups, a total of 68 cases, com-

pared with a similar graph of the third year of both groups shows clearly the trend toward lessening skin sensitiveness.

While no attempt is to be made here to discuss clinical results, it is of interest to point out in Table I that the more lengthy treatment does not diminish the clinical sensitiveness as much as it does the cutaneous. Certainly one would expect the best clinical results in those cases treated the longest, i.e., the four-year group, and the least satisfactory in the three-year group, whereas the opposite seems true.

TABLE I

CLINICAL RESULTS IN 1932 FOR EACH GROUP

	NUMBER OF DAYS OF SEVERE HAY FEVER SYMPTOMS		
	0	1-5	Over 5
Four-year group (30 cases)	53%	21%	24%
Three-year group (38 cases)	54%	31%	15%

From these figures certainly it is evident that the cutaneous reactions do not parallel the constitutional response to treatment obtained in any given year. Just why the poorer results were obtained in the group treated the longer is difficult to understand. It may be that the skin reaction, though diminished in intensity over that of previous years, was still too active to be a correct index to required treatment, and that larger doses than given were really necessary. Again it may be that these patients, being somewhat further removed from their previous untreated state which is the real criterion in evaluating results, found it difficult to furnish unbiased reports of their daily symptoms.

In these cases treated over a number of consecutive years, there occurs a diminution in the degree of sensitiveness as from A to B, B to C, or as in seven cases, A to C; or, infrequently, an increase from B to A, or C to B. These changes in sensitiveness occasionally may be explained as spontaneous variations, little influenced by treatment, as is commonly observed in a small percentage of any large group of pollen sensitive cases, usually in the earlier or later stages of their hay fever career. The great majority, however, seem to owe their diminution in sensitiveness to the persistent treatment.*

This change may probably be associated with a very gradual diminution in reagin production with a resultant decrease in general cutaneous sensitiveness. If this be so, it is reasonable to expect that, with the perennial type of treatment, these changes may take place more rapidly and to a greater extent. This probability is now being investigated.

*It may be that in the occasional case an increase in clinical sensitiveness is the result of the treatment, as we believe happens, though rarely, among patients treated perennially with large monthly injections. We have observed that in the course of treating individuals on an annual basis with monthly pollen injections, the degree of sensitiveness to treatment and to test may increase, because of or despite the treatment, so that doses of only one-half to one-third of the previous monthly maximum are tolerated, a successful degree of protection resulting, however, from a continuation of the monthly treatments at the new low level of dosage.

SUMMARY

A lessened degree of cutaneous sensitiveness may be demonstrated by intracutaneous test in cases of ragweed hay fever after three and four consecutive years of prophylactic treatment.

With the greater number of years of treatment, the lessening of the degree of cutaneous sensitiveness is more definite.

The change in cutaneous sensitiveness in these groups becomes more evident after the second consecutive year of treatment.

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(For discussion, see page 443.)

ATOPIC AND BACTERIAL ASTHMATIC PATIENTS

Some Immunologic and Histologic Evidences of a Fundamental Difference Between Them*†

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OUR studies have revealed that when asthmatic patients are tested immunologically for the appearance of a wheal in a passively sensitized skin site after dry pollen is sprayed in the nose, or histologically for the response to intradermally injected histamine, they fall into two general groups. These groups correspond to those obtained by clinical classification, namely, extrinsic atopic and intrinsic bacterial.

It is a common clinical experience to observe two asthmatic patients of approximately the same age, with similar histories, one of whom gives good skin tests to inhalants, foods or both, and fulfills all the criteria of atopy, while the other gives negative skin tests and cannot be proved to be atopic to any of the usual test substances. Most allergists assume that the latter type of case is due to bacterial sensitivity and classify the patient as a bacterial asthmatic. Such a diagnosis while serviceable for clinical purposes is by no means scientifically exact. It is a diagnosis by exclusion. While no one doubts that man can develop sensitivity to bacteria as a result of infection by those bacteria, there is no definite evidence of the relationship of this type of sensitivity to the symptoms in asthma. Reactions simulating the tuberculin reaction can be obtained in many asthmatic patients, as well as in many normal persons, following the intradermal injection of bacteria or their products. Occasionally also typical wheals associated with atopic reagins can be demonstrated on the injection of a bacterial antigen. Such reactions occur in patients in whom atopy to other substances can be demonstrated and in these there can be no doubt of the relationship of the reaction to the patient's symptoms since exacerbations of asthma and other typical symptoms of a constitutional reaction can be produced by injection of the antigen. Such observations have resulted in the opinion of some workers that bacterial atopy would be demonstrated with frequency if the proper bacterial test materials were available and that fundamentally all asthmatic patients, bacterial as well as atopic, are similar.

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*From the Asthma and Hay Fever Clinic of the Asthma, Hay Fever and Allergy Foundation.

†Read before the Ninth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Washington, D. C., May 6, 1933.

In 1930, in association with Ecker and Breitbart[1] we studied the rate of absorption of ragweed pollen from the nose in normal persons and in patients with hay fever or asthma not due to ragweed, using a modification of the Prausnitz-Küstner technic. The results of these studies indicated that there was a marked delay in the appearance of the wheal in the passively sensitized site in all patients in whom atopy could be demonstrated, while those with symptoms indistinguishable, but not demonstrably atopic, showed no delay but reacted like normal persons. In all, 12 atopic and 3 nonatopic persons were included in that report. Later[2] we confirmed these observations on 11 atopic and 12 nonatopic asthmatic patients, demonstrating similar differences between them following parenteral injection of the pollen. During the past several weeks we have continued these studies and are now able to report that a similar difference has been present in 24 nonatopic patients and in 27 atopic patients. We have observed two atopic patients in whom the passive transfer was poorly accepted as determined by injecting the transfer sites with dilutions of ragweed extract when no reaction had occurred in sixty minutes after spraying the pollen into the nose. These two cases are not included in the figures presented. In all other atopic patients with negative reactions at the end of one hour, the transfer areas reacted with ragweed solution in from 1:10,000 to 1:100,000 dilutions. The *sera used* were tested on the skin of one of us (M.B.C.) who always gives a characteristic reaction by nasal absorption within twenty minutes. Control of the serum is important, as not all clinically very sensitive ragweed patients have sera which give good reactions by this method.

In 1932, in association with Kline[3] we studied the histologic changes in allergic and nonallergic wheals, using the material and methods which will be described later.

Patients having hay fever or bronchial asthma due to ragweed pollen or house dust who were demonstrated to be markedly sensitive to the allergen by scratch and intradermal tests and whose blood contained atopic reagins sensitizing the skin of nonsensitive persons by the Prausnitz-Küstner technic, were used in this study. (The quantity of this reagin in the patients selected is now being determined.)

An area on the abdominal wall between the umbilicus and the crest of the ilium was shaved. Ragweed pollen extract in 1:10,000 dilution and dust extract in 1:10 dilution were injected intradermally to produce wheals 2 mm. in diameter. Histamine solution 1:100 was injected similarly in another area at least 7.5 cm. away from the area injected with ragweed. The injected areas were circled with ink so that they could be identified for removal at intervals after the surface phenomenon had disappeared.

Thirty minutes before the time for the removal of the specimen for histologic study a diamond-shaped area containing the two test wheals was blocked off at a distance not less than 5 cm. beyond the areas of reaction using 1 per cent novocaine. At the proper time, wedge-shaped pieces of skin and subcutaneous fat 1 by 3 by 1 cm. were removed from each wheal, care being taken to avoid the areas through which the ragweed extract or histamine had been injected. The tissues were fixed in 10 per cent neutral formalin.

For control purposes, specimens were removed in a similar manner from several persons who had hives after exposure to heat, cold, or scratching and from nonsensitive asthmatic persons in whom reactions were produced by histamine alone. The skin specimens were obtained by us in our office and were sent to Dr. Kline in numbered bottles so that purely objective histologic reports could be obtained.

Study of the sections revealed that the patients could be divided into two groups with respect to the response to histamine in skin specimens removed sixty minutes following its intradermal injection, and these groups corresponded to the clinical classification of atopic and nonatopic allergic patients. Whereas histamine produces in one hour severe reactions in the skin of atopic patients indistinguishable from those produced by atopens, reactions from similar amounts of histamine in the skin of nonatopic patients were minimal. It is important to point out in connection with these studies that we are dealing with reactions in the dermis and not with surface wheals. In most instances the surface phenomena of urticaria and erythema about the site of injection of histamine were as great in nonatopic as in the atopic patients.

A consideration of the results of these two studies shows that there are differences in the reacting capacity of the bodies of atopic and nonatopic persons, both to atopens and to histamine. These differences may be only quantitative or they may indicate some fundamental difference. Until there is definite proof of the exact relationships between atopic and nonatopic patients, it is necessary to classify them separately and to devise new methods for the study of nonatopic persons.

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SEDIMENTATION OF RED BLOOD CELLS IN ALLERGIC DISEASES

Report of a Study in 75 Cases*†

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UP TO the present time there has been reported no detailed study of the value of the sedimentation test in hypersensitive diseases. This investigation was made in an attempt to establish its value. There are only two recorded studies on the subject: a group of cases analyzed by Storm Van Leeuwen[1] in which he reports that practically 90 per cent (78 of 87 cases) had normal rates; and that of Schulhof[2] who found that about 85 per cent of his cases had unusually slow rates. The fact that the investigators used different instruments may account for the variation in conclusions. Although Cutler[3] states in a report of 5000 general examinations that allergic diseases do not influence the sedimentation rate, the control conditions of the study do not warrant absolute acceptance of the assertion. The chief defect of Schulhof's work is indicated in his statement that his study consists of "63 patients who undoubtedly or at least probably had allergic conditions." Of these 63, only 23 were definitely asthma or hay fever cases. Since the remaining 40 could easily have been other than allergic conditions, the value of the conclusion is reduced at least 50 per cent. Our results can be compared with Schulhof's because we used similar tubes and dilutions, although the readings are based upon the more generally accepted method of Westergren.

METHOD

Into a syringe containing 1 c.c. of 3.7 per cent sodium citrate, venous blood is drawn up to the 5 c.c. mark and well mixed. Tubes marked off in millimeters up to 100 are accurately filled to the 100 mark and placed in racks. The bore of the tubes is 3 mm. and the volume approximately 2 c.c. Readings for this study were made at 15, 30, 45, 60 and 120 minutes, at the end of twenty-four hours, and after centrifugation, to determine the packed red blood cell and white blood cell volume. Complete blood counts and serum protein contents were done on many for determining their relationship to the rate of fall and the blood cell volume in allergic diseases.

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†Read before the ninth annual meeting of the Society for the Study of Asthma and Allied Conditions, Washington, D. C., May 6, 1933.

All first determinations were made when the patient was admitted and tested. A repeat test was done one month after treatment was instituted, if the first rate was rapid, and at bimonthly intervals thereafter as indicated in all cases. X-ray examination of chest, sinuses and teeth and thorough search for upper respiratory and extrarespiratory infections were made on all patients as indicated. Home investigations by a trained worker were made to assist in the patient's care. Intracutaneous technic was used throughout for testing.

RESULTS

The average patient suffering from a purely allergic disease will show a normal rate of erythrocyte sedimentation, the term normal including those cases falling between 2 and 12 mm. per hour. In our series of 75 unchosen consecutive cases, 53, or 70 per cent, would be considered, on the basis of sedimentation rate, noninfective individuals. The remaining 22, or 30 per cent, showing abnormally high rates would be considered infective.

This arbitrary grouping on further investigations showed that two, or 5 per cent, with normal readings had demonstrable active infections present. In every case with high readings, we were able to find x-ray or clinical evidence of an active, acute or chronic infection.

When divided into groups according to the type of allergic disease present, the following graphs best demonstrate the results of the tests: (1) asthma; (2) hay fever; (3) nonseasonal coryza; (4) a graph is also shown of the sedimentation response in proved infective cases after alleviating the infection.

ASTHMA

A group of ten consecutive asthma patients without evidence of infection and ten complicated by infections was chosen to compile characteristic graphs. The noninfective group had a range of 3.5 to 10 mm. fall the first hour and a twenty-four-hour volume of about the same magnitude as the control cases.

In the infective group, the rate of fall was four times as rapid as in the noninfective or purely allergic cases. The summation of these ten curves is shown on Chart 1 in contrast to the control and noninfective cases.

HAY FEVER

A similar test of hay fever patients was made. The uncomplicated hay fever group of 21 cases was characterized by a slow rate of fall for two hours. The twenty-four-hour volume of red blood cells again fell to a perfectly normal level.

The three hay fever cases with associated infection, on the contrary, showed a rapid rate of sedimentation.

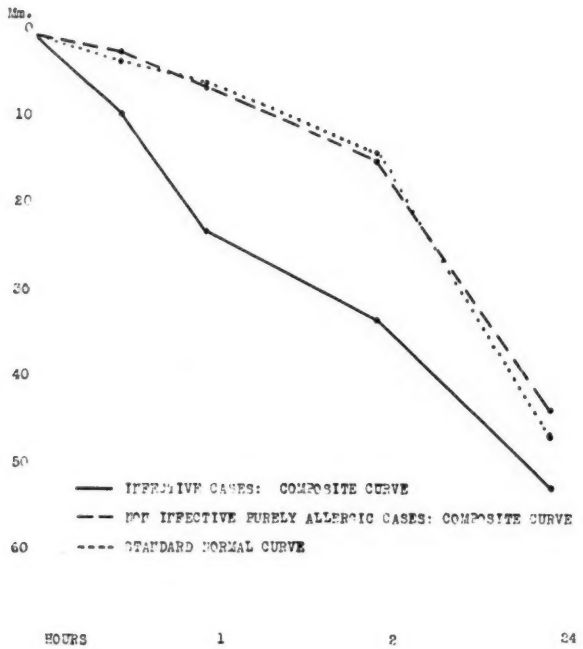

Chart 1.—Asthma.

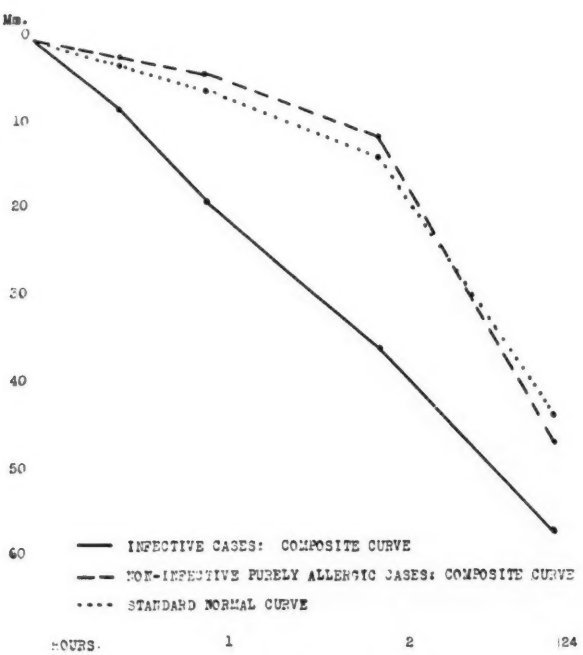

Chart 2.—Hay fever.

NONSEASONAL CORYZA

The greatest difficulty was encountered in separating the noninfective and infective nonseasonal coryza cases. Several patients showed sedimentation rates bordering on a high normal or a low increased rate. As the figures in Table I show, even after complete studies were done, it was impossible to be sure whether the infections found were responsible for the disturbing symptoms. It is conceivable to have infective foci present which are not the causative factors for the nonseasonal coryza. In choosing cases for this graph, we were influenced by the physical findings and x-ray examinations, as well as by the sedimentation rate; and, for that reason, some of the noninfective cases have rates which are just above the high normal limit. The composite curves show a less marked difference for this reason. As in the hay fever group, the noninfective cases had a normal rate of fall.

TABLE I

SEDIMENTATION RATES IN 75 PATIENTS WITH ALLERGY

DIAGNOSIS		NO. CASES	SEDIMENTATION RATE	
			SLOW	RAPID
Asthma Noninfective		16	16	0
Asthma & Infection		12	2	10
Hay fever		21	17	0
Hay fever & Infection		3	0	3
Nonseasonal coryza		12	12	0
Nonseasonal coryza & infection		7	3	4
Mixed types		4	4	0
Total cases	Noninfective	49	49	0
	Infective	22	5	17
	Mixed	4	4	0
Total %	Noninfective	65%	100%	0
	Infective	30%	23%	77%
	Mixed	5%	100%	0

RESPONSE TO TREATMENT

In a group of three characteristic cases of infective asthma and infective allergic coryza there is shown the return toward normal of the sedimentation rate following the attempts at removal of an infective focus. The reduction of these foci should always cause a change in the rate of erythrocyte fall, but not necessarily have any effect on the allergic symptoms. In the first two graphs the response was equally good in both symptoms and sedimentation rate. In the third case (A29475) there was only moderate relief from the asthma.

CASE HISTORIES

CASE 1. (No. 78411.) Infective asthma.

Present Illness. Woman aged sixty years who had suffered from asthma for fifty-five years and hives for fifty years. Foods were ap-

parently the cause of the hives in most instances. During acute infections the asthma symptoms would get much worse. For the past few

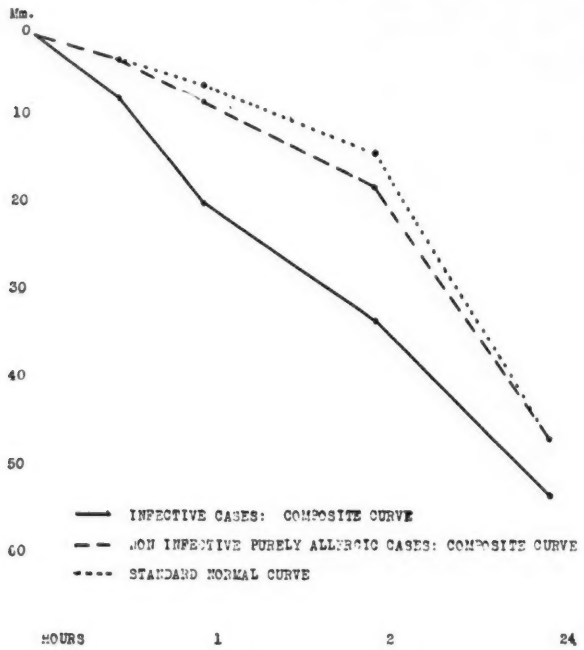

Chart 3.—Nonseasonal coryza.

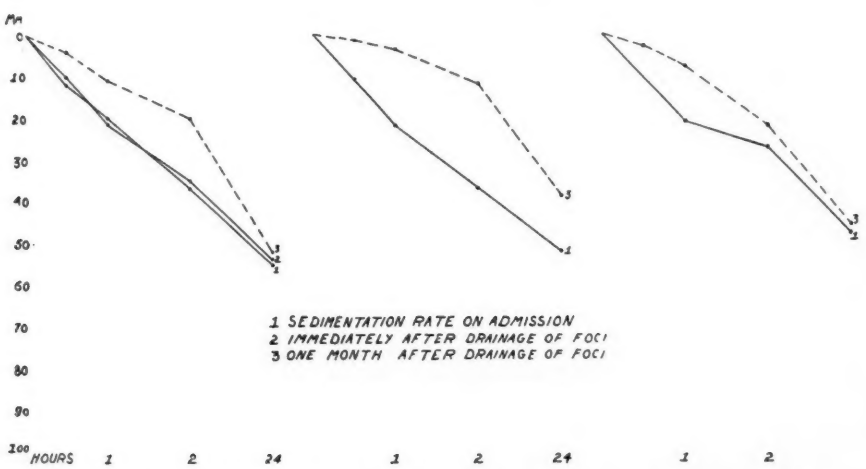

Chart 4.—Response of sedimentation rate to drainage of infective foci.

weeks she had suffered almost constantly with severe asthma. Adrenalin was needed frequently to afford relief up to her admission on August 30, 1932.

Past History. Always well except acute rheumatic fever in 1898.

Family History. No hypersensitivity.

Physical Examination. Fairly well developed elderly woman somewhat underweight and pale. Temperature 98.6°; pulse 80; respiration 20. Head, eyes normal; no adenitis. Nose, perforated septum and mucous membrane congestion; antra both transilluminate dully. Throat, negative. Lungs, many bubbling sonorous râles and wheezing expirations. Heart, normal; blood pressure 136/74. Abdomen, normal.

Laboratory Tests. X-ray examination of chest showed no evidence of tuberculosis but a diffuse bronchial thickening was present. X-ray examination of sinuses revealed markedly cloudy bilateral maxillary sinuses.

Blood Count. Hemoglobin 95 per cent. Red blood cells 5,030,000. White blood cells 13,000. Polymorphonuclear cells 74 per cent. Lymphocytes 26 per cent.

Blood Protein. Fibrin 0.42 per cent. Albumin 4.2 per cent. Globulin 2.9 per cent. Total 7.1 per cent.

Sedimentation Rate. First test on admission 20 mm. first hour. Second test immediately after removal of antral infection, 21.6 mm. first hour. Third test six weeks later, 11 mm. first hour.

Skin Tests. Moderate to house dust extract.

Progress. Up to the time of the antral drainages she became progressively worse and had no periods of freedom except with adrenalin. Within one month from the irrigations she was practically free of asthma and has been comfortable, a period of six months.

CASE 2. (35941.) Infective nonseasonal coryza.

A middle-aged man first seen at the clinic in November, 1932, stated that for many years he had suffered from a mild hay fever, but that since 1920 nonseasonal attacks of dyspnea, wheezing and cough had made him seek medical attention. The dyspnea was most marked at night and in the early morning. For several years he had constant rhinitis. All symptoms were aggravated after head colds and infections. The past history except for obstructed nasal breathing was irrelevant.

Family History revealed paternal hay fever.

Physical Examination. Normally developed and well nourished. Patient breathed through his mouth most of the time. Head, eyes normal. Nose, polypoid growth in the right nostril originating in the ethmoid; both antra transilluminate dully. Throat, clear. Teeth, no abscesses or dead teeth. Lungs, expiratory and inspiratory wheezing with coarse bubbling râles. Heart, blood pressure 160/90; no abnormality observed. Abdomen, negative.

Laboratory Tests. Sinus x-ray examination; dull antra and cloudiness in the right ethmoid. Right antrum shows a dull shadow in the floor.

Sedimentation Test. High rate 22 mm. the first hour.

Skin Tests. Marked to ragweed 0.01 mg. N. per cubic centimeter. Marked to dust concentrated ext. Marked to tobacco ext. Marked to codfish ext. Marked to chicken ext.

Progress. Following the removal of the polyps and antral irrigations there has been almost complete relief from symptoms. Treatments with ragweed and dust extracts and removal of the offending excitants were also accomplished. The second sedimentation rate shows the effect of this treatment on the suspension stability of the serum.

CASE 3. (A 37047.) Infective asthma with pulmonary tuberculosis.

Patient was a male, fifty years of age. At the age of ten years, he began to have seasonal attacks of wheezing and dyspnea with cough. At an early age these were accompanied by rhinitis and coryza which began about August 15 and lasted through October 15 or until frost. During youth he had frequent attacks of bronchitis but never any hemorrhages. He had been free from coryza between seasons until now, but asthma had been nonseasonal for several years. During the past four years he had five pulmonary hemorrhages, the last one in December, 1932. He had lost a moderate amount of weight, had frequent night sweats and persistent cough.

Family History. No tuberculosis or hay fever. One paternal aunt had had asthma and one sister had eczema.

Physical Examination. Temperature 98.2°; pulse 88; weight 131 pounds; 5 feet 5 inches tall. Fairly well nourished with moderate pallor of skin and mucous membranes. Throat, clear, and antra slightly dull to transillumination. Lungs show numerous course sonorous râles and hyperresonant percussion sounds. No subcrepitant apical râles. Excursion of diaphragm normal. Heart normal, with blood pressure 160/90.

Laboratory Tests. X-ray examination of sinuses was normal. X-ray examination of lungs revealed a generalized interstitial fibroid thickening and an old puerile type of tuberculosis apparently inactive. Skin tests revealed marked reaction to house dust and pears, with moderate reaction to goose epithelium, wheat, peaches and celery.

Sedimentation rate on admission was moderately increased and preceeded the last hemorrhage by ten days. A second test three months later showed a marked increase in spite of the absence of tuberculous symptoms or other evidence of complicating infections.

Note.—In spite of negative skin tests and absence of physical signs of active tuberculosis, the asthma became worse. The only evidence of increased activity of the infection present was the increased rate of sedimentation. He was then sent to the chest clinic for admission to a sanitarium where proper care could be exercised for both the tuberculosis and the allergic symptoms.

In addition to the sedimentation rate, on many patients we did complete cellular counts which revealed a close relationship between normal counts and normal twenty-four-hour volume of suspended cells. (Chart

5.) A total cellular volume of 48 per cent to 58 per cent in men and 45 per cent to 55 per cent in women is normal and indicates a red cell count of 4.25 to 5 millions per cubic millimeter and a hemoglobin correspondingly normal. Blood protein studies in 10 cases of uncomplicated hay fever patients failed to show any variation from normal to account for the relatively low rate of fall seen in many such allergic individuals. The present methods of determining fractional and total plasma proteins are variable over long periods of time and open to gross errors.* For this reason a more detailed study of the protein content and its possible relation to the suspension stability of the erythrocytes is being made.

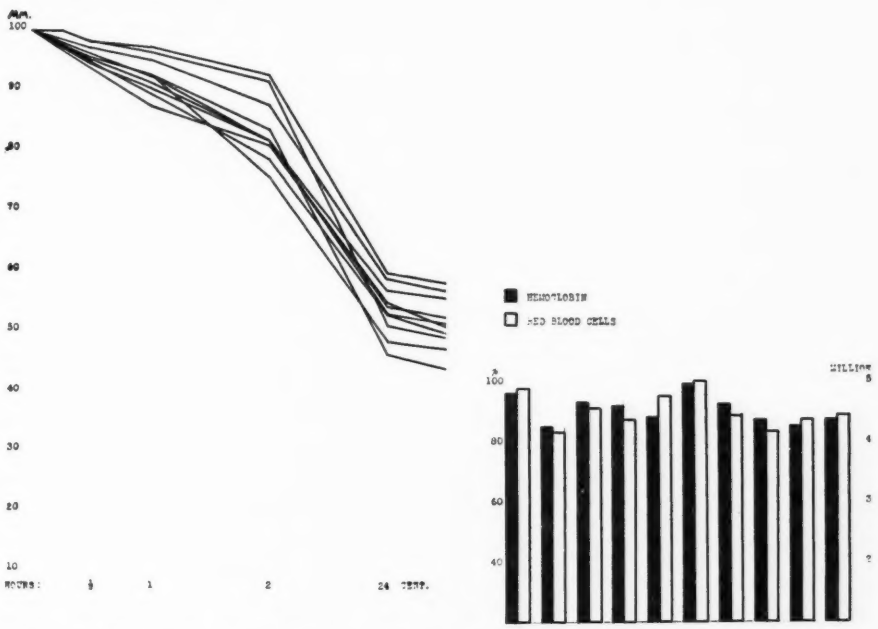

Chart 5.—Sedimentation rates on ten normal controls with hemoglobin and red blood cell counts.

The physiologic phenomena of sedimentation of erythrocytes depend upon some constituent or physical property of the suspending fluid rather than upon the cells themselves. This was well demonstrated by Kling[4] who compared the rates of fall in a patient's own blood serum and synovial fluid and by Forestier's[5] experiments of transfer of red cells from a pneumonia patient to the serum of a normal patient and finding a normal rate of fall in contrast with the high original rate. That sedimentation is not alone influenced by the protein volume is shown by the normal blood protein return in patients with both high and low rates. The physical character of either protein or fatty constituents may influence the fall of red blood cells by changing the elec-

*Personal communication with Miss M. Mattice, Dept. Laboratories, N. Y. Post Graduate Medical School and Hospital.

trodynamic balance (Schulten[6]). Crystaloids[5] are reputed to have no effect upon the suspension stability of red blood cells. The white blood cell volume may be roughly estimated by the white layer on the centrifuged column, and any gross abnormalities are easily detectable (Wintrobe[7]). Accurate estimates by this method are not obtainable for general use as is the erythrocyte volume determination. Variations in cell size will account for considerable range in normal cell volume when compared to cubic millimeter count determinations.

SUMMARY

1. The erythrocyte sedimentation rate in uncomplicated noninfective asthma, hay fever, or allergic nonseasonal coryza falls within the accepted normal limits and particularly in hay fever toward the low normal limit. It is, therefore, of little value as a test in purely allergic conditions.

2. Where an infection is present, the more acute the infection, the more rapid the drop.

3. In those instances where a high sedimentation rate is encountered, a very painstaking search should be made for infective foci as a possible primary or secondary cause of the symptoms. The presence of an infection may be simply of coincidental and not of etiologic significance.

4. A fairly accurate estimate of erythrocyte counts can be obtained from the twenty-four-hour or centrifuged specimen reading.

CONCLUSION

The sedimentation rate of erythrocytes is an aid in the differentiation of infective and noninfective allergic diseases. It is also of value in following the response to treatment in the infective group after the attempted removal of the foci.

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(For discussion, see page 451.)

BLOOD SEDIMENTATION RATE IN ALLERGIC DISEASE

A Study of 150 Nonselected Allergic Patients*

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THIS paper represents a study of the blood sedimentation rate in 150 patients, all of whom were patients of the Jefferson Allergic Clinic, and in all of whom the allergic diagnosis was definitely established. The purpose of this study was: first, to compare and check up our findings with the findings of other investigators on the same subject; second, to ascertain what additional information could be obtained from the study of sedimentation in reference to allergy; and third, whether the information so obtained would be of such value as to justify the making of this test a routine procedure in the study of allergic conditions.

The principles underlying the blood sedimentation and the theory behind variations in the rate so far remain unexplained. Different hypotheses have been advanced: increased fibrinogen content of blood plasma; some specific ferment in the plasma; electrophysical reaction; autoagglutination, just to mention a few, have been mentioned but not generally accepted (Cutler[1]). However, while the theory of the sedimentation remains obscure, the practical application of the test is well understood by now, and in this respect this test does not differ in any way from other well-accepted tests, as for instance the Wassermann test. It has been established with a reasonable amount of certainty that in healthy persons the amount of cellular destruction which accompanies the wear and tear of the body varies very little from day to day. The limits of those normal variations are well established. If, however, a destructive process is taking place in the body, the amount of tissue destruction increases considerably, and this, in certain diseases, seems to affect the blood in such a way as to cause the red cells to settle out from the plasma much quicker than in the normal healthy condition of the body. It seems that the more severe the disease, the quicker does the settling of the cells take place. According to Cutler,[1] those diseases are: (1) chronic infectious diseases, such as tuberculosis and syphilis; (2) malignancy; (3) localized suppurations, such as pelvic inflammations, suppurative mastoiditis, suppurative sinusitis, empyema of the gall bladder, bronchiectasis; (4) acute infectious diseases, such as pneumonia, septicemia, acute endocarditis, and the exanthemata.

*Read before the ninth annual meeting of the Society for the Study of Asthma and Allied Conditions, Washington, D. C., May 6, 1933.

The estimation of the rate of rapidity with which the settling of the cells takes place is the substance of the sedimentation test. So far, three methods for the performing of this test have been suggested: the Linzenmeier method, the Westergren method, and the Cutler method. While the findings by these three methods have been checked against one another and have been found comparable, only the Cutler method was used in this study, for the following reasons: (1) In the Cutler method definite and much shorter periods of time are used as compared with the lengthy and indefinite time periods of the Westergren method. (2) The divisions on the Cutler sedimentation tube are those of universally accepted measurements, as expressed in divisions of the cubic centimeter, instead of the arbitrary markings on the Linzenmeier tube. (3) Whereas by the Westergren and Linzenmeier methods only a single reading is obtained, the Cutler method supplies a more graphic and detailed description of the process which is taking place in the sedimentation tube. The Cutler method may be compared with the temperature, pulse and respiration curves, as seen on the history sheet; the other two methods may be compared with the single readings, as marked down by the nurse in her notebook. (4) The Cutler method is more universally used in this country, and so the findings by this method present a better opportunity for comparative study.

The technic of the sedimentation test by the Cutler method is very simple. One-tenth of one c.c. of 3 per cent solution of sodium citrate is gently mixed with 0.9 c.c. of blood in a 2 c.c. syringe and then poured into the sedimentation tube. The position of the sedimenting column is observed every five minutes for one hour, and the observations are recorded on a chart. Then a graph is constructed which shows the position of the sedimenting column at any given moment during the hour. It also portrays the changes in velocity that occur during the process of sedimentation.

In the fields of medicine in which the sedimentation test has been used widely and routinely, namely, in tuberculosis and gynecology, the investigators as a rule were interested in fast sedimentation rates only. Cases in which the sedimentation rate was not fast were of little interest to those investigators, and such cases were relegated to the so-called "normals" and were not studied to any great extent. Recently, however, K. Schulhof,[2] reported that, by using the Linzenmeier method in 610 nonselected patients, 115, or 19 per cent, had a rate much slower than that in healthy subjects; and that on further investigation of those 115 cases, he found that 53, or 46 per cent, of them had some form of allergic disease. Schulhof came to the conclusion that "it is evident that a pathologically slow sedimentation rate is found almost constantly in patients with allergic conditions." He also draws the conclusion that, in an allergic patient, a fast or even normal rate of sedimentation is indicative of the presence of some more or less serious complication.

Ordinarily, by the Cutler method, observations are made only for one hour. However, in order to be able to compare the above-mentioned findings of Schulhof with our own, it was decided to extend the usual one-hour observation by the Cutler method to two hours, because the Linzenmeier method used by Schulhof requires at least two hours of observation. We also wanted to make sure that we were not overlooking any changes that may become manifest during the second hour. In passing, it must be stated here that this additional hour of observation did not contribute any new information, and that the velocity of sedimentation during the second hour did not differ from that of the first: what was slow during the first hour remained slow during the second hour, and what was fast during the first hour remained fast during the second hour. According to their sedimentation rates, the patients in this study were divided in four groups: (1) slow, in which the rate was not more than 2 mm. by the end of the first hour; (2) normal, with a rate from 3 to 10 mm. by the end of the first hour; (3) moderately fast, from 11 to 20 mm. by the end of the first hour; (4) fast, more than 20 mm. by the end of the first hour.

The 150 cases studied here represent the following allergic conditions: asthma only—108, or 72 per cent; hay fever only 22, or 14.7 per cent; asthma and hay fever 14, or 9.3 per cent; chronic urticaria 1, or 0.7 per cent; chronic allergic rhinitis 4, or 2.6 per cent; chronic allergic conjunctivitis 1, or 0.7 per cent.

The sedimentation rates in those 150 cases were divided as follows: slow, 14, or 9.3 per cent; normal, 73, or 48.7 per cent; moderately fast, 48, or 32 per cent; and fast, 14, or 10 per cent.

The relation of the sedimentation rate to different allergic conditions in this group of patients is shown in Table I.

TABLE I

DISEASE	SEDIMENTATION RATE				TOTAL	
	SLOW	NORMAL	MODERATELY FAST	FAST	CASES	PERCENTAGE
Asthma	5	53	41	9	108	72.0
Hay fever	7	11	2	2	22	14.7
Asthma and hay fever	2	6	2	4	14	9.3
Allergic rhinitis		2	2		4	2.6
Chronic urticaria		1			1	0.7
Chronic allergic conjunctivitis			1		1	0.7
Total	14	73	48	15	150	
	9.3%	48.7%	3.2%	10%		100%

In analyzing Table I it will be seen that: (1) The number of abnormally slow cases is only 9.3 per cent of the total. All the rest are either normal or faster than normal. (2) While the percentage of hay fever cases in the entire group is 14.7 per cent of the total, the corresponding percentages of hay fever cases in the separate groups are as

follows: 50 per cent of the slow group, 15 per cent in the normal group, 4.2 per cent in the moderately fast group, and 13.3 per cent in the fast group; in other words, hay fever predominates in the slow group, whereas asthma predominates in normal and faster than normal groups.

There were in this series 80 white males and 56 white females, a total of 136 whites or 90.7 per cent; 8 colored males and 6 colored females, a total of 14 colored or 9.3 per cent. Their distribution, according to their sedimentation rate, is shown in Table II.

TABLE II

SEX	SLOW		NORMAL		MOD. FAST		FAST	
	W	C	W	C	W	C	W	C
Male	11	3	47	2	15	1	7	2
Female			23	1	27	5	6	

In analyzing Table II the only point of interest seems to be that while the females make up 41.3 per cent of the total number of cases, there were no females in the group with the slow sedimentation rate.

A detailed study of the patients in the slow group was undertaken. The composition of this group of patients in relation to allergic disease, race and sex are shown in Tables I and II. On the whole, they were a group of rather young people—only two were over forty years old. Their past medical histories were studied with especial reference to their previous operative record. This was done on account of reported fatalities after operations on patients with slow sedimentation rates (Schulhof[2]). In our group of cases with slow sedimentation rates 7, or 50 per cent, have had previous operations. Those operations range as follows: appendectomy 2, herniorrhaphy 1, radical mastoid operation 1, tonsillectomy and adenoidectomy 7, circumcision 1; otherwise their medical histories were nonrelevant.

The physical examinations were negative in all cases in this group, except for some wheezing in the asthmatics; their blood pressures were the usual low blood pressure rates of the average allergic type. One patient had a plus four Wassermann and was under treatment at the time of the testing. The x-ray findings were as follows: In one case there was infection of the teeth; in 7 cases there was cloudiness of the sinuses. Definite increase of root shadows and peribronchial thickening were reported in 7 cases. In 4 cases the diaphragm was deformed by adhesions. In one case the changes in the lungs were reported to be those of bronchiectasis. In 1 case, in a man forty-five years of age, an old healed tubercle in the right upper lobe was reported. On the whole, the physical findings in this group were those usually found in allergic patients.

The largest group of patients in this study, the group with normal sedimentation rates, did not present anything of special interest. It might be worth while mentioning, in passing, that in this group of 73 patients there were 9 cases with well-healed tuberculous lesions of the childhood type (calcified glands); 2 diabetics; 2 cases of hypertension, the causes for which were not established; and one case of pneumoconiosis.

In the group with the moderately fast sedimentation rate, consisting of 48 patients, there were 2 cases of syphilis; 5 cases of well-healed tuberculosis of the adult type; 1 case of active tuberculosis with positive sputums and corresponding x-ray findings; 1 case of an enormous lung abscess in the right lower lobe, with exudative tuberculous changes in both apices; 1 case of early aneurysm of the aorta; 2 cases of nephritis; and 3 cases of diabetes.

In the group with the fast sedimentation rate, out of a total of 15 cases, 4, or 26.6 per cent had tuberculosis. There was 1 case of severe hypertension, the cause for which was not established.

The frequency of positive skin reactions findings in these 150 patients according to their blood sedimentation rates, as well as the distribution of sinus disease and lung changes in the same groups are shown in Table III.

TABLE III

SEDIMENTATION RATE	SLOW	NORMAL	MODERATELY FAST	FAST	NO.
Number of cases	14	73	48	15	150
Positive skin reactions	14	57	44	13	128
Diseased sinuses	7	45	32	11	95
Lower lobes infection					
Deformed diaphragm	4	17	15	4	40
Tuberculosis	0	0	2	4	6

In analyzing Table III it would seem that: (1) The largest percentage of patients who gave no positive skin reactions was in the group with the normal blood sedimentation rates. (2) The incidence of sinus disease was 50 per cent in the slow group, 61.6 per cent in the normal group, 66.6 per cent in the moderately fast, and 84.6 per cent in the fast sedimentation group. (3) All cases of tuberculosis in this series of 150 patients occurred in the moderately fast and in the fast sedimentation groups.

Attention must be called to the fact that this study of blood sedimentation in allergic patients took place at a time of the year when the hay fever patients in this series were not actually suffering from hay fever. What changes, if any, may take place in their sedimentation rates during the hay fever seasons will form the subject of future studies.

SUMMARY

1. In a series of 150 allergic patients, in all of whom the allergic diagnosis was definitely established, there were only 14 patients with abnormally slow sedimentation rates, or 9.3 per cent of the total.

2. There was a predominance of hay fever cases in the group with slow sedimentation, and a predominance of asthma in the normal and faster than normal groups.

3. No female patients in this series of 150 cases had a slow sedimentation rate.

4. Fifty per cent of the patients with abnormally slow sedimentation rates had been operated upon previously with no bad after-effects.

5. The physical findings in the patients with slow sedimentation rates were in no way different from the average findings in allergic patients.

6. A normal sedimentation rate in allergic patients is not indicative of the presence of some more or less serious complication.

7. Allergic patients with moderately fast and especially with fast sedimentation rates, ought to be studied very carefully in order not to overlook any accompanying condition, especially tuberculosis.

8. While the sedimentation test is nonspecific in its nature, it is important in that an abnormally fast sedimentation rate seems to be indicative of a serious destructive process in the body and acts as a timely warning signal. As such, it deserves a place among the routine laboratory procedures.

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2022 SPRUCE STREET.

(For discussion, see page 451.)

SO-CALLED URINARY PROTEOSE IN INDIVIDUALS ALLERGIC TO RAGWEED*

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WHEN, in 1930, Oriel and Barber[1] reported the finding of a foreign substance in the urine of allergic individuals during the attack, to which the individual manifested specific skin sensitivity and serum sensitiveness demonstrable on passive transfer, it appeared hopeful that a method had been evolved which would facilitate rapid discovery, if not identification, of the offending pathogen. This abnormal urinary substance resembled proteose in its reactions and appeared to be specific for the allergic reaction in a manner comparable to the specificity of allergens as they are demonstrated on cutaneous testing. The substance appeared to have very high antigenic titer; since, for therapy, it was usually necessary to dilute it 1,000 or 10,000 times, and occasionally 1,000,000 times. The results of treatment were reported as very promising. The suggested explanatory hypothesis is that the original antigen combines with some reactive substance in the liver producing a secondary, changed antigen which, however, still possesses antigenic specificity.

Following Oriel and Barber's original technic, without change, we attempted to isolate urinary proteoses from six cases with intractable asthma, vasomotor rhinitis, or allergic dermatitis. Urine specimens were collected under chloroform during attacks. The precipitate obtained was alkalinized according to directions and made up into dilutions of 1:100 and higher. No patient gave stronger than borderline reactions to the concentrated 1:100 extract. With the first cases treatment was started with the higher dilutions and run up to 1:100 strength. On the later cases treatment was started with 1:100 strength. None of the six patients was improved with this therapy, and none manifested exacerbation following the treatment.

Nothing further was done with this procedure until the extremely favorable reports of Darley and Whitehead[2] and of Mills and Martyn[3] seemed to indicate that the method should be investigated in further detail. Feeling that the logical procedure would be to study cases of known etiology, we proceeded to isolate so-called proteose specimens during the 1932 ragweed season from individuals known to be sensitive to ragweed. Some who had had no previous symptoms gave strongly positive cutaneous reactions to ragweed extract and were having symptoms

*Presented before The Society for the Study of Asthma and Allied Conditions, Washington, D. C., May 6, 1933.

at the time. Some had had previous desensitization and were virtually symptom free during the season.

Proteoses were obtained from 21 ragweed sensitive patients during the ragweed season. For one reason or another the study was not completed on 7, leaving 14 for study. Of these 14, 5 had had no previous treatment, while 9 had been on perennial treatment. Five were having symptoms at the time the proteose specimen was obtained, while 9 were not. Of the 5 who were having symptoms all gave a negative reaction to their own proteose in the concentrated form (1:100). One of these proteoses showed up one plus on passive transfer, but was negative both on the original patient and on another known to be extremely sensitive by skin test to ragweed.

Ten of the 14 patients were tested with their own proteoses. All gave negative reactions to 1:100. Of these 10, 7 gave positive skin test to ragweed, 3 negative. Proteose tests throughout were done by the intracutaneous method, with 1:100 concentration. Control ragweed tests were always by the scratch method (1:50).

The five patients who were having symptoms at the time of collection of proteose specimens and who gave positive skin reactions to ragweed and negative to their own proteose, were further tested by passive transfer into skin areas sensitized to ragweed and by testing on other individuals known to give strongly positive cutaneous reactions to ragweed. Two reacted negatively both in actively and in passively sensitized skin. One was negative in an active skin and one plus in a passive skin. One was negative in an active skin, not tested passively; one was negative in a passively sensitized skin but not tested in an active skin.

Four of the patients gave positive skin reactions but were having no symptoms at the time of proteose collection. They were all negative to their own proteose. Two were also negative on passive transfer and to testing on an unusually sensitive skin. One was negative on an active skin and one plus on passively sensitized skin. One was negative on an active skin, not tested on a passive skin.

No reaction with a concentrated so-called proteose at any time was of sufficiently positive character to produce whealing. The one plus positive reactions are represented only by flares.

In two cases treatment with the autogenous proteose was undertaken for relief of symptoms due to ragweed. One, an asthmatic two plus sensitive to ragweed and having symptoms at the time of collection, received seven injections of 1:1,000 proteose without benefit. The other, suffering from hay fever, three plus sensitive to ragweed and also sensitive to sunflower, had received no relief from coseasonal ragweed desensitization. He received four injections of 1:100 autogenous proteose without improvement but was promptly relieved after cutting down the sunflower in his garden.

We may say then that within the limits of the study, proteoses obtained from ragweed sensitive individuals during the ragweed season failed to give specifically positive skin reactions by testing either on the particular individual or on another very sensitive ragweed case or by passive transfer. This was true even with individuals who were having pollinosis symptoms at the time of collection. In two cases, no relief was obtained from autogenous coseasonal daily proteose therapy. Passive transfer was always checked by obtaining simultaneous positive reactions to intracutaneous ragweed extract, in the passively sensitized areas.

The pollen season 1932 was one of low prevalence, the highest peak being 135 on September 6. The counts on the days on which proteose specimens were obtained ranged from 8 to 42. In nine of the fourteen instances the average daily count at the time of collection was over 20. Our experience has been that an average daily count of five may be sufficient to produce symptoms in an untreated sensitive individual. Obviously, however, the threshold for symptoms varies depending upon the degree of sensitiveness.

In January, 1933, Trasoff and Meranze[4] reported negative results from a clinical study of urinary proteoses in bronchial asthma. Our findings in regard to pollinosis appear to be in agreement with theirs. While these authors state that they attempted to determine the presence of a proteose, they do not state what method they used; although they did conclude that there is a substance in the urine of asthmatics, reported by Oriel as "proteose." In our own study during the ragweed season we made one slight change from our earlier method. Oriel and Barber precipitated their ethereal extract with an equal volume of alcohol. They do not mention the percentage of this alcohol, and since our original results had been negative, we used absolute alcohol throughout the ragweed experiments. Otherwise the technic agreed in every detail.

All specimens gave a positive Millon reaction for protein. However, since the extracts were all made up in saline to which 0.5 per cent phenol had been added, this reaction could be accounted for by the presence of phenol. The Biuret test consistently gave a color change, but the change was of a bluish tint rather than the characteristic violet or pink of proteose. The xanthoproteic reaction was not determined, since like the Millon reaction it is rendered positive by the presence of the phenyl group. Total nitrogen determination showed an average of 11.3 mg. per 100 c.c. in the 1:100 concentration from those having allergic symptoms at the time of collection, and 13.7 mg. from those without symptoms at the time of collection. The estimated average total twenty-four-hour output of so-called proteose in these two groups is 5.5 and 7.0 mg. Oriel and Barber report that the daily proteose nitrogen excretion in the normal nonallergic individual ranges from 7

to 25 mg. daily. In pemphigus, it ranges from 65 to 88; in psoriasis from 113 to 142.6; in asthma prurigo from 49 to 290. In active tuberculosis it was 122; inactive, 70. In inactive rheumatism it was 20, while in acute rheumatism the daily output of proteose nitrogen was 159. In a case of urticaria, it was determined at 64.2.

We may say then that in addition to failure to obtain clinical improvement with so-called proteose therapy and failure to obtain specific positive skin reactions, we were unable to demonstrate an increase in total urinary nitrogen.

The suggestion appears appropriate that, should Oriel and Barber continue to report positive results at the present time in contrast to these negative results, any attempt to reconcile the two conclusions should be based primarily upon the utilization of only such extracts as might show an increased proteose nitrogen following its preparation.

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(For discussion, see page 429.)

ANAPHYLACTIC MANIFESTATIONS IN CANCER*

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ALTHOUGH the subject of anaphylaxis has been investigated extensively in the so-called anaphylactic diseases, such as hay fever and bronchial asthma and to some extent in the infectious diseases, notably tuberculosis, comparatively little is known of anaphylaxis in cancer.

During the observation of a large number of cancer patients it is not uncommon to find anaphylactic manifestations, such as urticaria, angioneurotic edema, and vasomotor skin disturbances (*dermographismus albus*). A recent striking example in which the onset of severe anaphylactic manifestation followed the development of cancer of the breast and became more marked when the disease recurred, suggested a possible relation between the two states.

That the presence of anaphylactic manifestations in patients suffering from cancer may be more than a mere coincidence is suggested also by a recent report of Auler,[1] who observed several patients exhibiting signs of severe anaphylactic disturbances soon after the clinical onset of the malignant process, although the patients had never shown similar symptoms previously. It seems logical to suspect that a cancer patient may become hypersensitive or anaphylactic to his own tumor, thus gradually becoming hypersensitive to others of the known anaphylactogenic agents. A pursuit of this conception seemed to us especially warranted since certain experimental studies support clinical observations in pointing to the possibility that tumor-bearing persons may be in an anaphylactic state.

The purpose of this investigation was to ascertain what clinical and experimental evidence can be accumulated in support of and against the presence of either local or general anaphylaxis in cancer.

LOCAL ANAPHYLAXIS

Local anaphylaxis in experimental cancer has been reported by several authors. V. Dungern and Coca[2] (1909) in their study on sarcoma of the hare found this tumor to be readily transplantable to rabbits. A second transplantation of the tumor into a previously inoculated rabbit, however, proved not only to be unsuccessful but also was followed by a marked inflammatory reaction, which, according to the authors, was due to the development of a local hypersensitivity in the tumor-bearing

*From the Tumor Clinic and the Nelson Morris Institute of the Michael Reese Hospital, Chicago, conducted under a grant from the Cancer Research Institute of Chicago.

animal. Two years later (1911) Weil[3] observed that inoculation of the Flexner-Jobling adenocarcinoma into normal rats was not followed by any inflammatory reaction. Tumor-bearing animals, however, responded to a reinoculation by an intense local inflammatory reaction. The author interprets this phenomenon as being analogous to the Arthus phenomenon and to the local allergic reactions described in human beings.

Ravenna[4] in 1912 reported 21 cancer patients tested intradermally with an extract prepared from a carcinoma of the breast of which 6 reacted positively while 12 control patients all reacted negatively. Intracutaneous tests in carcinoma were tried also by Boyksen,[5] using the Abderhalden serum; i.e., serum of horses previously inoculated with carcinoma. He reported 21 cancer patients, of which 17 reacted positively with the formation of a hemorrhagic wheal, while among 46 controls only two positive reactions occurred. Boyksen's findings have been partly confirmed by Sulger,[6] who in 52 cancer patients found the reaction to be positive in 60 per cent, while only one positive reaction was observed in numerous controls. Wigand[7] tested 13 cancer patients, of which 4 reacted positively, while all of 7 controls reacted negatively. Similar results were obtained by Druegg.[8] Of 13 cancer patients tested, 8 reacted positively, while all 7 controls reacted negatively.

Eggers[9] failed to substantiate Boyksen's observations. In more than 250 tests he found the reaction negative in 25 per cent of cancerous patients and positive in 25 per cent of control patients and therefore unreliable for clinical purposes. Harke[10] also denied the practical value of Boyksen's reaction since the percentage of positive reactions in 23 cancer patients and 84 controls was about the same, varying between 27 per cent and 56 per cent, depending upon the quality of the immune serum.

Serum of cancer patients previously irradiated with x-rays was used by Mertens[11] for a diagnostic intradermal reaction. Four of 8 cancer patients reacted positively, while 4 controls reacted negatively. Mertens' findings were partly substantiated by Hoff,[12] who found the reaction positive in all of his 14 cancer patients, but also positive in 5 of 24 controls. Auler[1] reported allergic skin reactions obtained in the majority of cancer patients tested with an aqueous carcinoma extract from which the alcohol, ether, and acetone-soluble substances were removed.

From this evidence it seemed to us that the question as to whether or not cancerous human beings exhibit a local anaphylactic reaction to the inoculation of cell-free cancer extracts is of sufficient interest and possible importance to merit further investigation.

TECHNIC

Finely divided carcinoma tissue was extracted with physiologic saline solution in a ratio of 1:5 to which 0.5 per cent phenol was added. Ex-

traction took place in an incubator at 37° C. for one week. The extract was centrifuged and the supernatant fluid passed through a Berkefeld filter. Sterility tests were performed. Two-tenths cubic centimeter of the cell-free extract was used for intradermal skin tests. Tests have been made with extracts derived from various carcinoma tissues. An extract prepared from a bronchogenic carcinoma, however, yielded the most satisfactory results and was used in all the experiments. All tests were made on the flexor surface of the forearm. The reaction was read after twenty-four hours. A slightly elevated, intensely red wheal or papule of a diameter from 2 to 6 mm. was interpreted as a positive reaction. The reaction remained for several days and disappeared gradually. Control tests with 0.5 per cent phenol in physiologic saline solution were made, always with negative results.

The test was made on 60 patients, 35 of whom were suffering from definitely proved carcinoma and 25 from various noncancerous diseases.

TABLE

	CASES	NO. POSITIVE REACTIONS	NO. NEGATIVE REACTIONS	PER CENT POSITIVE
Cancer	35	22	13	62.8
Controls	25	6	19	24.0

Out of 35 patients (see Table) suffering from carcinomas of various origin, such as larynx, antrum, breast, lung, esophagus, pancreas, colon, rectum, and uterus, the test was positive in 22 patients and negative in 13 patients. The negatively reacting group was affected with cancer of the uterus, stomach, papilla of Vater, antrum, esophagus, and lungs. Of 25 controls of various noncancerous diseases, the test was positive in 6 patients whose diagnosis was: Coronary sclerosis, myocarditis (in two patients), Buerger's disease, fracture, and fibroadenoma of the breast.

DISCUSSION

The difficulties in interpreting these results are apparent. A positive percentage of 62 per cent in cancer cases compared with 24 per cent positive results in control cases renders the test in its present form useless for clinical diagnostic purposes. Whether or not better results may be obtained with a further refinement of the technic and a better understanding of the underlying nature of the test awaits further study. Since Hektoen and his coworkers[13] in 1923 succeeded in producing not only species specific, but also organ specific antibodies by using the globulin fraction of a thyroid extract, it is likely that the globulins are the site of specific organ antigens, a view supported by Witebsky[20] and others. Our efforts to render the reaction more specific by using the globulin fraction of the carcinoma extract (the possible carcinoma specific antigen), however, failed to yield better results. Marangos[14] recently

issued a preliminary report of skin tests on cancer patients performed with a high-molecular fatty acid derived from carcinoma tissue. All of his 23 cancer patients examined reacted positively; of 17 controls only 3 reacted positively.

In our series, the fact cannot be neglected that the test was positive three times as frequently in cancer as in other diseases. This apparent prevalence of an increased hypersensitivity of cancer patients to cancer extracts is suggestive, in our opinion, of an anaphylactic response on the part of the cancerous patient. The question whether the reaction is specific in the sense of a true antigen-antibody reaction cannot be answered a priori and is largely dependent upon the demonstration of an anaphylactic antibody, as will be discussed later.

GENERAL ANAPHYLAXIS

As early as 1909 Pfeiffer[15] developed the theory that a cancer patient during the course of the disease becomes hypersensitive or anaphylactic to his own tumor. Thus he develops anaphylactic antibodies not only against his own tumor, but also against carcinomatous tissue in general. Pfeiffer furthermore assumed that the unrestrained carcinomatous growth and the formation of metastases may be due to the gradual development of the anaphylactic state which affects not only the serum but likewise all the cells and tissues of the organism. Pfeiffer attempted to substantiate his theory by the demonstration of anaphylactic antibodies in the blood of cancer patients. He claimed that cancer juice injected into guinea pigs which had been sensitized by the serum of cancer patients forty-eight hours previously, caused a definite anaphylactic reaction, but when normal human serum was injected previously, no reaction occurred. A rapid fall in the temperature of the guinea pig of several degrees was considered a definite sign of an anaphylactic reaction.

Although Pfeiffer's findings have not been confirmed generally,[16] we considered that it might be possible to produce a passive anaphylaxis in guinea pigs with the serum of those cancer patients who had shown a positive skin reaction, on the assumption that their serum in particular may contain anaphylactic antibodies.

A series of 6 guinea pigs was tested. Each of 4 guinea pigs was sensitized with 4 c.c. of serum of cancer patients while 2 guinea pigs, used as controls, were sensitized with normal serum. Forty-eight hours later the cancer extract was injected. In none of the animals could an anaphylactic reaction be noted. Careful registration of the temperature of the animals did not reveal any marked fall, while a mild fall of about 1° C. was observed to occur frequently after any intraperitoneal injection, as was also found by Ranzi.[16] Thus, no positive results were obtained by this experiment.

At this point it was thought interesting to repeat Ransohoff's[17] experiment, in which he found that blood serum taken from cancer patients and injected into guinea pigs which previously had been sensitized by the serum of cancer patients, caused no, or a very weak, anaphylactic reaction, while normal human serum, when injected into the sensitized guinea pigs, produced the usual violent reaction. In repeating this experiment with 4 guinea pigs, 2 of them reinjected with cancer serum, 2 with normal serum, we were unable to note any difference in the behavior of the guinea pigs, all of them offering the same usual anaphylactic reaction. Also, Green[18] in a large series of experiments could not confirm Ransohoff's observation.

DISCUSSION

It appears, therefore, from the results that our experiments fail to demonstrate anaphylactic antibodies in the blood of cancer patients. This fact, naturally, does not exclude the presence of an anaphylactic condition in carcinoma. It may be, for example, that anaphylactic antibodies in carcinoma are of such a labile or fragile composition that they readily become destroyed and cannot be demonstrated with our present methods. It should be recalled that even in tuberculosis, a disease with a definite local and systemic anaphylactic response, passive transfer has not yet been established convincingly (Coca[19]), the nature of the tuberculin test, the clinical value of which is well established, therefore, still being under discussion. Further clinical and experimental observation of cancer patients will be necessary before definite conclusions can be drawn as to a local or systemic anaphylactic response in carcinoma.

CONCLUSION

Clinical and experimental data are offered as to a local and general anaphylactic response in carcinoma. It appears that the existence of an anaphylactic condition in cancer is probable, although no experimental proof of a true anaphylaxis in the sense of an antigen-antibody reaction can be demonstrated at present.

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A MILK-, CEREAL- AND EGG-FREE DIET FOR ALLERGIC INFANTS*

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SINCE 1925 we have been feeding certain allergic infants on a milk-, cereal- and egg-free diet. This diet was developed to enable us to control infantile eczema and other manifestations of allergy in infants who developed symptoms while nursing from the breast, or while taking cow's milk, either unchanged or in some one of its modified forms.

Allergy in infants manifests itself early in life as eczema. It begins usually between the tenth week and the sixth month. In many infants colic, diarrhea, and vomiting precede the onset of the eczema or are complicating symptoms. Numerous studies have demonstrated that sensitivity to foods is the chief cause. The older the child at the time of testing, the more likelihood there will be of demonstrating the etiologic agent by skin testing. In children or young adolescents who have not lost their infantile eczema, or who have developed the next stage of atopic eczema (neurodermatitis), positive reactions to the causative agents are almost universally demonstrable. In these children atopic reagins can be demonstrated by the Prausnitz-Küstner reaction in almost every instance when a positive skin reaction is obtained.

Since allergy to foods is the chief cause of infantile eczema, the foods ingested in the greatest amount are usually the ones which become the excitants of the allergic reaction. For this reason cow's milk is the most frequent offender. Some infants begin to have eczema while nursing from the breast; in others, it begins when supplementary feedings of cow's milk are added or when milk or some one of its various modifications is substituted completely for mother's milk. In the former instance, the allergen may be any food eaten by the mother, since it has been shown that foods eaten by normal mothers may be excreted unchanged in their milk. (Donally.[1]) The quantity excreted depends in part on the quantity ingested, and since cow's milk is urged on nursing mothers as an article of diet, it is frequently ingested by the infant. Cereals and eggs often reach the infant in a similar manner. If eczema begins when cow's milk is added to the diet, the cause is obvious and this substance is the sole cause in many young infants. When orange juice, cereals, egg, and vegetables are added to the diet, certain other

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infants begin to get symptoms. In their order of frequency milk, cereals, and eggs are the most common offenders. Often eczema is caused by several foods. A large amount of either one of them will produce symptoms, or eczema may result from the additive effect of small doses of several. Under these circumstances, for example, a child may have tolerance for eight ounces of milk, or one egg, or one tablespoonful of cereal daily. If the amount of one of these foods or the amount of two or more ingested during a day's time is less than the total atopic tolerance, no symptoms will result. The child receiving subreacting doses is said to be in allergic equilibrium or in the balanced allergic state. (Vaughan.[2]) When in this balanced allergic state because of cereals, for example, an additional dose of milk added to the effects of the previously ingested cereal overbalances the tolerance and symptoms result. For such an infant reduction of the amount of milk ingested or the alteration of the formula by using acidified, boiled, or powdered milk may effect a cure. Likewise, in those infants in whom the sensitivity is slight, and especially in those sensitive only to the lactalbumin in milk, some modification of the formula suffices, since it has been known for years that heating, drying, and certain chemical actions would alter proteins sufficiently to change their antigenic properties. However, these changes are slight, and in clinical practice modifications of cow's milk have only a narrow field of usefulness since we now have acceptable substitutes for milk. The real reason for continuing to feed cow's milk has not been ignorance of its etiologic relation to the eczema, but because no adequate substitute was known which was generally available. Allergists have devised milk-free diets for infants and have fed them successfully for a number of years but the difficulty of preparing them at home has limited their general trial by other clinicians. Following the demonstration that soy bean protein was adequate for the nutrition of normal infants, and the introduction of an infant food prepared from it, many milk-sensitive children have been fed on this substance with control of the eczema in the majority.

Because of the common association of milk, egg, and cereals in the causation of eczema, we have been using a diet consisting of beef, cauliflower, tomatoes, carrots, spinach, cane sugar, olive oil, cod liver oil, gelatin, calcium lactate, acid sodium phosphate, and water which contains 19 calories per ounce. This mixture forms a complete food containing all of the mineral salts and vitamins in excess of the amounts necessary for normal development.

Table I shows the foods used in its preparation and the calculated analysis based on published reports.[3] Beef was used as the chief source of protein because it contains lysine, cystine, tyrosine, tryptophane, phenylalanine, and histidine, the amino acids listed by Sherman[4] as necessary for growth. Beef has the added advantage of possessing

TABLE I

FOOD ANALYSIS OF DIET RECOMMENDED

AMOUNT	FOOD	PROT.	FAT	CARB.	CALCULATED CALORIES	CA	MG	K	NA	P	CL	S	FE	SOURCE OF COMPOSITION	A	B	C	D	E	P.P.	SOURCE OF VITAMINS
75 gm.	Beef (round)	15.97	5.92		117.16	0.009	0.019	0.270	0.067	0.172	0.060	0.183	0.0024	Rose[3]		+	?	?	+	++	Hawk and Bergeim[6]
150 gm.	Cauliflower	1.65	0.15	4.95	*27.75	0.184	0.021	0.333	0.102	0.091	0.075	0.129	0.0009	Rose[3]	+	++					
150 gm.	Tomatoes	1.80	0.30	6.00	33.90	0.016	0.015	0.412	0.015	0.039	0.051	0.021	0.0006	Rose[3]	++	+++	+++				
100 gm.	Carrots	1.10	0.40	9.30	45.20	0.056	0.021	0.287	0.101	0.046	0.036	0.022	0.0006	Rose[3]	++	+	var. +				
50 gm.	Spinach	1.05	0.15	1.60	11.95	0.033	0.018	0.387	0.062	0.034	0.037	0.019	0.0018	Rose[3]	+++	+++	+++			+	
3 cups	Water																				
35 gm.	Sugar			35.00	140.00				—					Rose[3]							
22 gm.	Olive oil		22.00		198.00									Rose[3]					+		
4 gm.	Cod liver oil		4.00		36.00										+++			+++			
10 gm.	Gelatin	9.14	0.01		36.65																
4 gm.	Calcium lactate					0.734															
5 gm.	Sodium acid phosphate								1.619	1.092											
1000 c.c.	Total	30.71	32.93	56.85	646.61	1.032	0.094	1.690	1.966	1.474	0.258	0.374	0.0063								
100 c.c.		3.071	3.293	5.685	64.66	0.1032	0.0094	0.169	0.196	0.147	0.0258	0.0374	0.00063								
100 c.c.	Human milk	1.50	3.30	6.50	60.70	0.034	0.005	0.047	0.010	0.015			0.0002								

Figures used are for edible portions; the food was weighed raw.
*Composition of cauliflower from Lily's Chart.[5]
Iron for human milk from Wheeler and Wheeler.[9]

pellagra-preventive vitamin and is always available. Carrots and cauliflower were selected because of their calcium content. Spinach was used as a source of iron and vitamins, and tomatoes for vitamin C and flavor. Cane sugar and olive oil were added to increase the carbohydrate and fat content respectively to approximate the amounts found in human milk. Gelatin was added to emulsify the fat. Calcium lactate and acid sodium phosphate were added in amounts necessary to bring the total calcium to 1 gram and phosphorus to 1.5 grams to each quart of the formula. This quantity meets the requirements of Sherman and Hawley[5] for children. It is an excess of the amount in human milk, because these authors found the utilization of calcium and phosphorus from vegetables less than that from milk. Cod liver oil was added to insure the best use of the available calcium and phosphorus.

This diet has been used for a period of from one to twelve months in twenty patients. The infants varied in age from eight weeks to eleven months at the beginning of the trial. All were allergic, presenting the symptoms of severe and intractable eczema alone or accompanied by allergic coryza and asthma. All had been fed various modifications of diets, using cow's milk as their base. Some were in a good state of nutrition; others presented a picture of inanition subsequent to periods of semistarvation, which had been advocated in attempts to clear up the symptoms. At first the diet was used only in the hospital where its preparation could be supervised by the dietary staff; later individual mothers were taught to prepare it for their children and during the past several months through the cooperation of Mr. L. D. Johnson of Mead Johnson & Company we have had it available in liquid form for distribution to our patients.

The following description of the product as prepared by Mead Johnson & Company shows that the calculated analysis from published reports (Table I) compares favorably with the actual analysis of the commercially prepared product:

Proximate percentage of ingredients:

	Per Cent
Beef	9.1
Cauliflower	10.9
Tomatoes	10.9
Carrots	7.3
Spinach	3.6
Cane sugar	2.3
Olive oil	2.0
Cod liver oil	0.3
Gelatin	0.7
Calcium lactate	0.7
Sodium acid phosphate	0.2
Water	51.7

The beef was ground and mixed with the previously washed and finely cut cauliflower, tomatoes, carrots, and spinach. The water was added and the mixture was placed in a double jacketed steam kettle. It was tightly closed and the air was removed by means of a vacuum pump. The mixture was then cooked by steam introduced into the outside jacket. This method of cooking minimizes the loss of vitamins through oxidation during the cooking. The mixture was then strained and mixed with the rest of the ingredients, consisting of cane sugar, olive oil, cod liver oil, gelatin, calcium lactate, and sodium acid phosphate. This entire mixture was then homogenized and poured into jars, sealed, and sterilized.

Chemical Analysis:

	Per Cent
Protein	3.1
Fat	3.2
Carbohydrates	5.6
Ash	0.7
Moisture	87.4
	100.0

Inorganic Constituents:

	Per Cent
Calcium	0.07
Magnesium	0.01
Sodium	0.10
Potassium	0.14
Phosphorus	0.14
Chlorine	0.02
Sulphur	0.03
Iron	0.0038
Copper	0.00075

19 Calories per ounce.

Every child began to gain weight shortly after beginning to take the feeding and continued to do so during its use. There were no digestive disturbances, no diarrheas, no symptoms of vitamin deficiencies, and development was regular and orderly. In all except one the skin manifestations were controlled completely within a few weeks. The nasal and bronchial symptoms in those under eleven months of age were also controlled. In some of the older infants there were sensitivities to inhaled factors which proved to be of clinical importance in the production of symptoms. One child, whose history follows, was sensitive to one of the vegetables in the diet and this was removed and another substituted.

CASE REPORT

R. W., aged eleven months, was referred to us on March 17, 1930, because of an intractable eczema involving the entire body, complicated by periodic attacks of asthma. The eczema began at one month of age while on mother's milk. At six weeks of age, because of the continuation of the eczema and the presence of severe abdominal cramps with vomiting, he was taken off the breast and a milk formula

was given. These conditions failed to improve and a three months' period of hospitalization followed, during which time various diets were tried. Periods of starvation were always followed by improvement in the symptoms, but they recurred in a severe form following all of the feedings tried. At the age of eight months attacks of asthma, typical of those seen in infants, began. These would last for from one to three days and were often accompanied by fever. There was usually a period of freedom between attacks of from two to three weeks. At about this time, also, attacks of hives began to be noted. There was a bilateral family history of allergy.

Physical examination revealed an emaciated infant of eleven months. The skin was dry, thickened, purplish-gray in color, covered in some places by crusts, in others, by exuding serum. The head, neck, thorax, and arms were most severely involved, although there were lesions scattered over the remaining skin. The respirations were labored and were accompanied by wheezing. The child could not sit up, had no teeth, and weighed sixteen pounds. There were no other gross abnormalities.

The egg-, milk-, and cereal-free diet previously described was begun. The mother prepared it at home. Within four days there was a gain in weight of ten ounces, but the eczema was unchanged. At the end of ten days the general condition was improving, but the eczema persisted. This led us to substitute turnip for the spinach in the diet and, since it was felt that various substitutions might have to be made, the child was hospitalized. During a thirteen-day stay in the hospital there was a gradual improvement in the skin condition, and the asthma cleared up. On discharge from the hospital he weighed eighteen pounds and three ounces. From this time on there was progressive increase in weight and improvement in the eczema which disappeared completely within six weeks. The asthma which persisted was found to be due to sensitivity to dog hair and house dust, and control of contact with these factors was followed by its disappearance. In May, teeth began to appear, and at eighteen months of age, there was full complement of teeth for that age, the weight was twenty-six pounds, and the child appeared normal in every respect. When the symptoms had been controlled for six months, additions to the diet were made progressively and for the past several months he has eaten a full diet with the exception of milk, egg, and one or two vegetables which are still capable of producing symptoms. Also, as is usual in allergic children, there has been a progressive development of clinical sensitivity to several new inhalant factors, so that he now has both grass and ragweed hay fever for which he is under treatment. He now weighs forty pounds at three and one-half years of age and is symptom-free.

No one diet is suitable for all allergic infants since, having the capacity to develop sensitiveness, they become allergic to new substances which they receive in large amounts and which they have been able to tolerate. For this reason several well-tolerated complete dietary substitutes for milk should be available.

SUMMARY AND CONCLUSIONS

A milk-, cereal- and egg-free diet, adequate for growth and nutrition, containing all the known vitamins has been described.

Allergic infants thrive when placed on this diet. In the vast majority, the allergic symptoms disappear. Progressive additions to the diet are

then made. For those infants whose symptoms do not clear up, it is necessary to search for causes among the foods in this diet by substituting for it a soy bean food, and to search for inhalant causes.

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INCIDENCE OF ASTHMA IN 400 CASES OF CHRONIC SINUSITIS*

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WHEN one reads the literature dealing with the relationship of asthma and paranasal sinus disease, it becomes evident that the term "sinusitis" does not have a clear-cut meaning. Thus, in discussions dealing with the frequency with which sinus disease is associated with asthma, one writer[1] states that he found evidence of sinus disease in 26 per cent of his cases of asthma and another[2] in 90 per cent. It is not probable that the incidence of sinus disease varies over such wide limits. It seems reasonable to assume that different criteria on which the diagnosis is made must account in a large part for these relatively low and very high figures.

Reports of the incidence of sinusitis in some four thousand cases of asthma have appeared in the literature. The following may be taken as representative studies. Chobot[3] found evidence of sinus disease in 40 per cent of 117 children who had asthma. In a more recent study[4] of 84 asthmatic children he found the incidence increased to 67 per cent. Rackemann and Tobey,[5] in a study of 1,074 patients with asthma, found evidence of sinus disease in 44 per cent. Adam[6] found nasal and sinus pathology in conditions of sufficient degree to demand treatment in 60 per cent of 640 asthmatics. It would seem conservative to consider that about one-half the patients who have asthma may be expected to have sinus disease associated with it.

Pathologic studies, such as those of Hansel,[7] seem to demonstrate conclusively that the changes which take place in the sinus mucosa, in these cases of sinusitis associated with asthma, are identical with those which take place in the bronchial mucosa.

Very little information is available as to the frequency with which sinus disease occurs in the general population. The textbooks seem to be silent on this subject. Kern and Donnelly[8] found that 72 per cent of 50 normal "controls" (in Philadelphia) showed x-ray evidence of pathologic conditions in the sinus. Duke[9] found definite evidence of sinus infection in 6 per cent of 100 bank employees on routine examination.

The statement is frequently made that sinusitis occurs in 100 per cent of the population. Of course, this is true if the mild sinus inflammation

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which occurs with every "common cold" is taken into account. However, such a sinus inflammation has no more clinical significance than the pharyngitis which is associated with the "cold," and deserves separate classification no more than does the pharyngitis.

An attempt to arrive at some answer to this question was made by studying the records of 103,000 patients admitted to the Strong Memorial, the Rochester Municipal, and the Rochester General Hospitals from 1926 to 1932, inclusive. These are all general hospitals. Private as well as ward patients are admitted to the Rochester General and Strong Memorial Hospitals. This seems to represent the general population of the community as well as can be expected of any group of hospital patients. Ten thousand of these admissions represent newborn children and are therefore excluded from this consideration.

A diagnosis of sinusitis was made in 1,100 of the remaining 93,000 patients, or 1.2 per cent. Only a very small proportion of the patients was admitted to the hospitals for treatment of the sinus disease alone. In almost all, the diagnosis of sinusitis represented but one of several pathologic conditions found in the patient. Patients whose histories or routine physical examinations presented evidence suggesting sinus disease, were examined in the otolaryngologic and x-ray departments. Most patients who had disease conditions which might be explained on the basis of focal infections also received such special examinations.

With the exception of the very small number of patients who were admitted with acute sinusitis, the absence of subjective symptoms related to the sinuses was very striking. Sinus pain and sinus tenderness were almost never present. In fact almost the only complaints were made by patients who had foul smelling nasal discharges, and those who had nasal obstruction.

It is appreciated that 1.2 per cent cannot be claimed as representing the true incidence of sinus disease in this group, because not all the patients received the special examinations necessary to confirm a diagnosis of sinusitis. Without doubt the lack of subjective symptoms also contributed to the failure to make the diagnosis in some patients. However, it seems proper to suggest that this figure may approximate the proportion of the population who will present evidence of sinus disease at any given time, of a grade sufficient to warrant recording as a diagnosis on a hospital record. Such a classification is not one which can be used with great precision, but it seems to be the only one applicable to this study.

In the past 10 years several papers have been published which have dealt with the frequency with which sinus disease is found in asthmatic patients, but I have been able to find but little information as to the incidence of asthma in cases of chronic sinusitis. Dennis[10] states that of 60 patients who had sinus disease, 28 (46.6 per cent) had asthma.

To study this question, 400 of the patients who were found to have evidence of sinus disease were selected. The criteria on which the selection was based were as follows:

(1) The sinus disease must have been present at least one year.

(2) There must have been evidence of various combinations of the following: (a) purulent secretion in the nose or nasopharynx over long periods of time; (b) nasal polyps; (c) definite x-ray evidence of abnormal shadows in one or more sinuses, confirmed by clinical evidence of disease, such as loss of translucency on transillumination, or washing purulent material from the sinuses, etc.; (d) evidence of sinus disease sufficient to warrant radical sinus surgery.

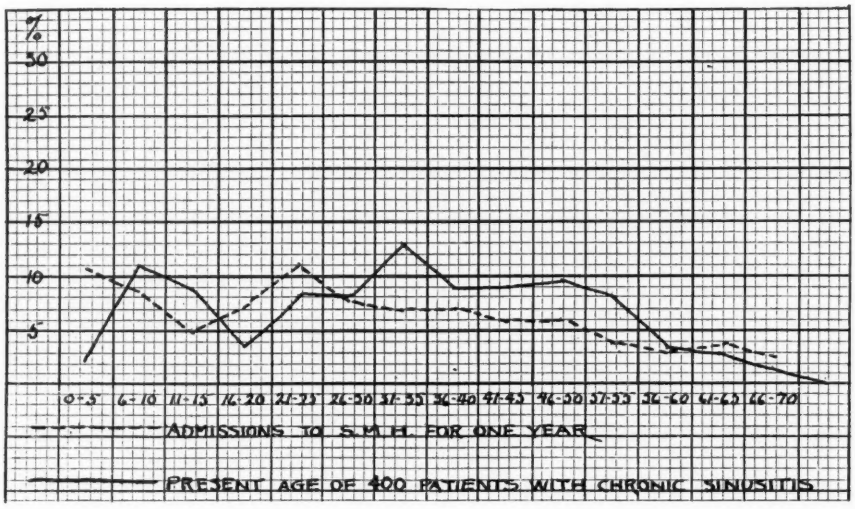

Chart 1.

An attempt was made to classify the patients as to whether the sinusitis was of the purulent or hyperplastic type, but this was found to be impractical. Many patients who were followed over long periods had purulent material in their sinuses at one time, no pus at a later date, only to have a recurrence of pus still later.

The patients were divided into five-year groups as to age. There are two definite peaks in the curve representing these age groups, one in the group from six to ten years (11 per cent), and another from thirty-one to thirty-five years (13 per cent). The first rise may be caused by the fact that children are first subjected to mass contact in school at about this age and are especially likely to suffer from upper respiratory tract infections thereby. No such theory can account for the rise in the latter part of the fourth decade, however, and I have no explanation to offer. Nor can an explanation be offered for the drop in the curve between the ages of ten and twenty years, except that it coincides with

the time when the adolescent tends to become more free from the "colds" which occur so frequently in childhood. The relatively high level of the curve from about the age of thirty-five years to that of fifty-five years is worthy of note.

The question at once arises as to whether the high and low points in this curve can be related to the number of patients in the several age groups admitted to the hospitals. To answer this, the patients admitted to the Strong Memorial Hospital for one year were divided into five-year groups according to age, and a similar curve was drawn. Comparable figures for all the patients were not available because the hospitals classify the patients in other than five-year age groups to satisfy the requirements of the State Department of Charities. However, the numbers of patients admitted to all the hospitals in the various age groups were so nearly alike that this curve very well represents the whole group.

It is evident that the high points in the curve representing the incidence of sinusitis in the six to fifteen and thirty to fifty year age groups do not result from mere hospital admissions at these ages.

Because dyspnea of the asthmatic type is so frequently associated with such conditions as chronic bronchitis and bronchiectasis, the incidence of these conditions in this group of patients was noted. It is well known that evidence of sinus pathologic conditions has been found in a large proportion of the patients suffering from these forms of pulmonary disease.

TABLE I

400 PATIENTS WITH CHRONIC SINUSITIS (DURATION AT LEAST 1 YEAR).

	Females ----------217—54%
	Males ----------183—46%
	105 patients (26.25%) presented evidence of some form of nontuberculous pulmonary disease.
ASTHMA	49 patients (12.25%)
	14 of these patients had had asthma for several years prior to the onset of the sinus disease;
	35 (8.75%) had sinus disease which preceded, or coincided with, the onset of asthma.
CHRONIC BRONCHITIS	42 patients (10.05%) (12 also had asthma)
BRONCHIECTASIS	31 patients (7.75%) (5 also had asthma)

Slightly more than half the patients in this group were females. The sexes were equally represented in the 93,000 hospital admissions. One hundred five patients (26.25 per cent) presented evidence of some form of chronic nontuberculous lung disease. Forty-nine patients (12.25 per cent) had asthma. They ranged in age from four to seventy-three years. Three-fifths of them were thirty or more years old and about one-quarter were over fifty.

Because of the lack of subjective symptoms related to the sinuses, it was difficult in many cases to get reliable histories as to the time of

onset. However, in 21 of these 49 patients the date of onset of the sinus disease could be stated with considerable accuracy. In 14 (8 extrinsic, 6 intrinsic), the asthmatic symptoms preceded the sinus disease by several years. In 7 (all intrinsic), the sinus disease preceded the asthmatic symptoms by from two to ten years. In the remaining 28 patients (26 intrinsic, 2 extrinsic), the two disease processes appeared at about the same time.

These facts seem to confirm what has been stated by several writers, namely, that the condition which tends to produce asthma in an individual may also tend to bring about pathologic changes in the mucosa of his nasal sinuses, and vice versa, and that in a large proportion of the patients in which the two conditions are found, it is improbable that the sinusitis, in itself, is the cause of the asthma or that the asthma is responsible for the sinus changes.

Forty-two patients (10.05 per cent) had chronic bronchitis. Of these, 12, or nearly one-third, also had asthma, all intrinsic.

In 31 cases, a diagnosis of bronchiectasis was made. Of these, five, or one-sixth, also had asthma. One of the five was pollen sensitive, the remainder being intrinsic cases.

CONCLUSIONS

Among 93,000 admissions in three large, general hospitals, 1.2 per cent showed enough evidence of disease of the paranasal sinuses to warrant a diagnosis of "sinusitis" on the hospital records. It is probable that this figure at least approximates the proportion of this community which will show evidence of sinus disease of the same grade, at any given time.

Chronic sinusitis occurs at all ages, except the very youngest. It seems especially likely to occur in the later half of the first decade of life and from the age of thirty to fifty or fifty-five years.

In the study of 400 cases of sinus disease of at least one year's duration, two facts are outstanding. Almost three-fourths of the patients had no evidence of disease of the lungs in spite of the long-continued infection in the upper respiratory tract. On the other hand, about one-fourth had some form of chronic, nontuberculous pulmonary disease, such as asthma, chronic bronchitis, or bronchiectasis. No other disease condition carries such a threat to the integrity of the lung tissue, regardless of whether or not the sinus disease is considered as the sole cause of the pulmonary disease.

The fact that only 12.25 per cent of the patients with chronic sinus disease had asthma, indicates strongly that chronic sinusitis per se is not a frequent cause of asthma. This becomes even more evident when one considers that only 8.75 per cent of the patients actually had their asthma begin at the same time as the sinusitis or later.

By the same reasoning, it seems proper to conclude that chronic bronchitis, with an incidence of 10 per cent in these patients with chronic sinus disease, and bronchiectasis, with an incidence of 7.75 per cent, are rather infrequently dependent solely on disease of the paranasal sinuses for their causation.

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VASOMOTOR RHINITIS TREATED WITH PURE CARBOLIC ACID

Preliminary Report

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IN OCTOBER, 1932, Chandler[1] reported the cure of hay fever by the application of phenol to the nasal mucosa in over one hundred cases. The technic he describes is as follows: "A long probe slightly bent, the end of which is covered by a pledget of cotton carefully wound around the probe and saturated with pure carbolic acid, is passed through one side of the nasal passage through a nasal speculum clear into the nasopharynx and is carefully withdrawn so that the end of the probe goes up as high as possible in the nares and along the side of the septum. Another saturated probe is then inserted only in the anterior nares so as to be sure and coat the entire surface of the anterior part of the nares with special attention to the inferior turbinated bone. This same process is then repeated in the opposite side."

Although the results in the above mentioned hay fever cases were very gratifying, it is difficult to agree with Chandler when he says that, "Pure carbolic acid applied to the mucous membrane of the nares desensitizes the membranes."

In anaphylaxis the term "desensitization" denotes the subdivided, graduated doses of the second injection of the antigen in a previously sensitized animal, which causes all traces of sensitization to be obliterated. In human hypersensitivity, permanent desensitization has not yet been achieved as is shown by the annual treatment of hay fever, where only a temporary desensitization is accomplished, and which is termed by Cooke[2] hyposensitization or partial exhaustion of sensitivity, because when the treatment is discontinued, reactions to the pollens reappear at a later date, and the patient must be reinjected. Therefore, it is inconceivable how a sensitive mucous membrane in the human being can be desensitized by the application of phenol.

What then is the rationale of the phenol treatment in hay fever or vasomotor rhinitis? In order better to understand the mechanism of the treatment, it would be seemly to give a short review of the nerve supply of the nose. The olfactory bulb which lies on the cribriform plate of the ethmoid bone, gives off branches to the mucous membrane of the septum and the nasal fossae. These are the special nerves of the sense of smell. The fifth or trifacial nerve, as it leaves the brain, enters the gasserian

ganglion, which is lodged at the petrous portion of the temporal bone, and is then subdivided into three large branches, the ophthalmic, the superior maxillary, and the inferior maxillary. The first two are sensory nerves, and the third is both motor and sensory. The nasal nerve, which is a branch of the ophthalmic, supplies the mucous membrane and the outer wall of the nose. The superior maxillary gives off a nasal branch, which supplies the integument, and joins with the nasal branch of the ophthalmic. Two branches from the superior maxillary nerve descend into the sphenomaxillary fossa and enter the sphenopalatine ganglion. The sphenopalatine ganglion is placed in the sphenomaxillary fossa and possesses a sensory root from the nerves of the superior maxillary, a motor root from the facial nerve, and a sympathetic root from the carotid plexus of the sympathetic. The last two join and form the vidian nerve, which enters the ganglion. The sphenopalatine ganglion gives off branches which supply the mucous membrane and the bones of the nose.

From this rough description of the innervation of the nasal mucosa, it is apparent how impulses or stimuli are carried from the nose to the brain centers and back again through the efferent nerves. It would seem therefore, that rather than desensitize the nasal mucosa, this treatment either partially or wholly blocks the nerve endings in the mucous membrane of the nose, and stops afferent impulses from being carried to the nerve centers, thereby giving relief from symptoms.

This experimental study of the phenol treatment was done both in my office and at the Asthma and Hay Fever Clinic of Lebanon Hospital on 16 cases of vasomotor rhinitis and two of asthma. Some of these cases were complicated by seasonal hay fever, and others by chronic sinusitis with polypoid degeneration. I have not yet had the opportunity to apply this treatment to uncomplicated seasonal hay fever.

CASE REPORTS

CASE 1.—Miss L. F., aged thirty-four years, applied for treatment on November 27, 1931. She complained of perennial rhinitis since 1930 and also from persistent, severe headaches. She showed sensitivity to some of the trees, grasses, and weeds and also to some of the foods. She herself noted that the foods to which she was sensitive, aggravated her condition whenever she partook of them. She was treated with pollens from December, 1931, to January, 1933, and the offending foods were omitted from her diet, with but indifferent results. On January 10, 1933, phenol was applied to the nasal mucous membrane. A grippy feeling followed the application, lasting one day, but she noted that the headache entirely disappeared. On January 13 she felt much better; there was no sneezing, no rhinorrhea, only a slight pain over the right temple. Improvement continued, with the exception of the pain over the right temple, until January 21, when a slight rhinorrhea recurred. Phenol was again applied to the nares and from then on to this date the symptoms entirely disappeared.

CASE 2.—Mrs. B. K., aged thirty-three years, applied for treatment in October, 1930. She had been suffering from sneezing, rhinorrhea, and clogged nose, also

dyspnea complicated by seasonal hay fever for the past five years. Tests with pollens gave but indifferent reactions; orris root, some of the inhalants, and also some of the foods gave marked reactions. She was treated with the pollens and with orris root until January, 1933, and although there was some improvement in her condition, yet the sneezing and nose block would persist intermittently every week. On January 24 the phenol application was made to the nasal mucous membranes, and from that date she has been entirely free from all symptoms, except on February 7, when she sneezed for a little while.

CASE 3.—Mrs. J. G., aged thirty-eight years. She applied for treatment in April, 1931, and gave a history of perennial rhinitis complicated by seasonal hay fever for the past ten years, and continuous asthma for the last three years. She reacted to all the pollens of the trees, grasses, and weeds, also to dust and some of the other inhalants, and to a few of the foods. In spite of all treatment with dust and pollens, the asthma was persistent and severe, and the hay fever was but little improved during the season. Phenol was applied on January 25, 1933, and from then on although she still has occasional spells of asthma, they are not severe, and not prolonged as previously, and her nose symptoms have entirely disappeared.

CASE 4.—Mr. B. C., aged forty-six years, applied for treatment January 9, 1933. He gave a history of coughing and wheezing since infancy. On December 1, 1932, he had a severe attack of asthma. From then on he had been sneezing, sniffling, and coughing constantly. He also complained of seasonal hay fever from July to the frost, and reacted to the pollens of the weeds and plantain. As the nose symptoms were persistent, phenol was applied on January 18; for one day his nose was completely blocked, then on January 20 his nose cleared, he could breathe better, and his head felt clearer. Most noteworthy, the asthma stopped. The improvement continued until February 6, when he again complained of a slight nose block. Phenol was again applied and he felt free from all symptoms thereafter.

CASE 5.—Mrs. A. S., aged forty-six years, applied for treatment in December, 1929. She complained of sneezing, rhinorrhea, and clogged nose since childhood. Skin tests were mostly negative. Treatment with pollens and vaccines gave only moderate improvement. Phenol was applied on January 25, and since then the attacks of sneezing have been much lessened.

CASE 6.—Mrs. A. M., aged twenty-eight years, applied for treatment January, 1929. She gave a history of asthma since childhood, and rhinorrhea since 1928. She reacted to the pollens of some of the trees and weeds and very markedly to cotton. She was treated with pollens, and though there was relief from the asthmatic attacks, the wheezing continued. On March 7, phenol was applied to the nares and since then she has felt better.

CASE 7.—Mr. E. A. W., aged forty-two years, registrar of the Asthma and Hay Fever Clinic of Lebanon Hospital, applied for treatment on January 15, 1933, suffering from chronic rhinitis and frequent head colds for the past two years. Phenol was applied to the nasal mucosa on the same day. The after-effects were headache and nasal congestion for two days. The symptoms have entirely disappeared, his nose is clear, he breathes freely, and has had no colds since then.

CASE 8.—Mrs. D. S., aged thirty-three years, applied for treatment March, 1929. She gave a history of perennial rhinitis for the past seven years. Examination of the nose showed congested mucous membrane and left ethmoiditis; she was sensitive to dust, some foods, and some inhalants. Treatment with dust and vaccine gave but little improvement. On April 11, 1933, phenol was applied. The usual grippy feeling followed on the next day and then improvement set in. On April 20 her symptoms slightly recurred and phenol was again applied. She feels better although the time is too short to make any prognosis.

CASE 9.—Miss R. F., aged sixteen years, applied for treatment on October 10, 1930, suffering from vasomotor rhinitis. She showed sensitivity to dust, feathers, and some foods. Treatment with autogenous dust gave poor results. Phenol was applied on April 3, 1933. The after-effects were headache, nose block, and occasional nose bleed for two days. Although there has been apparent relief from symptoms, the time is too short to make any prognosis.

CASE 10.—Mrs. R. W., aged forty-nine years, applied for treatment October 21, 1929, and gave a history of vasomotor rhinitis and asthma for two years. All tests were negative, and after nonspecific treatment with pollens, vaccines, and nasal tampons for three and a half years, there was some improvement in the asthma. Her sneezing, however, was not relieved. On March 6, 1933, phenol was applied to the nares with after-effects of burning sensation and obstruction of the nose for two days. She has been relieved of her symptoms since.

CASE 11.—Mrs. E. W., aged thirty-one years, applied for treatment on January 15, 1931, suffering from vasomotor rhinitis and dyspnea. All tests were negative, and she received nonspecific treatment with pollens and nasal tampons for two years. The results were poor. Phenol was applied on March 3, 1933, with after-effects of headache, clogged nose, and pain in the nose, lasting three days. The sneezing stopped and her condition has remained good.

CASE 12.—Mrs. F. S., aged forty-nine years, applied for treatment on April 1, 1932, after suffering from rhinitis for one year. She was sensitive to dust and some of the foods. Treatment with autogenous dust and nasal tampons gave no improvement. On February 24, 1933, phenol was applied to the nares, and for the following three days she suffered from complete nasal obstruction. Relief in this case was only slight.

CASE 13.—Mrs. E. K., aged thirty-three years, applied for treatment on February 26, 1932, after suffering from vasomotor rhinitis for one year. She showed sensitivity to dust, and was treated with dust and nasal tampons for one year, with but poor results. Phenol was applied on February 20, 1933. The after-effects were headache, nasal obstruction, sore throat, and pain on swallowing, for five days. Examination showed white patches on the posterior pillars of the tonsillar fossae, possibly due to oversaturation of the cotton on application. The patches disappeared in about three days. She was, however, relieved of all symptoms until March 20, when sneezing recurred and phenol was again applied. To this date her condition is good.

CASE 14.—Mrs. R. W., aged forty-five years, applied for treatment on November 27, 1931, suffering from perennial hay fever. Tests showed sensitivity to dust, orris root, and some foods. She was treated with dust and orris root with but indifferent results. On January 13, 1933, phenol was applied to the nasal mucosa. The after-effects were headache, nasal obstruction, and occasional nose bleed for one week. The symptoms were only moderately relieved.

CASE 15.—Mrs. P. B., aged forty-three years, applied for treatment on July 16, 1928, and complained of vasomotor rhinitis and asthma. She was sensitive to pollens of the weeds, to dust, and to some foods. She was treated with autogenous dust and pollens for four years; the results were poor. Phenol was applied to the nares on January 19, 1933, and the after-effects were severe headache and nasal congestion for three days. The sneezing stopped immediately and has not returned, but the asthma persists.

CASE 16.—Mrs. S. H., aged forty-four years, applied for treatment on February 16, 1931, and gave a history of continual sneezing for five months. Tests showed

sensitivity to autogenous dust and to some foods. She was treated with her own house dust for a period of two years, with very little improvement. Phenol treatment was applied on January 13, 1933. The after-effects were severe headache and nose block for one and one-half days, but the sneezing stopped immediately. She was practically free from all symptoms thereafter.

CASE 17.—Mrs. D. G., aged thirty years, applied for treatment in November, 1932. She had been suffering from continuous asthma, with severe attacks since May, 1930. Tests with inhalants and foods gave only slight or moderate reactions, and treatment consisted of vaccines and sulphur-oil, with the result that the continuous asthma was changed to the intermittent type, with attacks about once a month, lasting three or four days. On March 21, 1933, phenol was applied to the mucous membrane of the nose, but her condition remained unchanged.

CASE 18.—Miss E. W., aged twenty-eight years, applied for treatment in April, 1932, and complained of continuous asthma since 1929, complicated by fall hay fever. Reactions to pollens and other foreign proteins were either negative or slight. Examination of the nose showed chronic ethmoidal sinusitis with polypoid degeneration. Treatment consisted of vaccines and sulphur-oil, with no improvement. On June 8, 1932, she was admitted to the Lebanon Hospital, where she suffered from asthma continuously until June 23, when a Caldwell-Luc operation was performed and the polyps were removed. That night she almost died from an asthmatic attack and oxygen had to be administered. The next day her condition improved, and she was free from asthma until September 2, when the attacks returned, and were so severe that adrenalin had to be injected about five or six times a day. On March 25, 1933, phenol application was made to the nose; at the same time treatment with sterile distilled water intravenously was started. Since then her condition is much improved, and she needs adrenalin only once every second or third day. In this case one is unable to say whether the distilled water or the phenol caused the improvement. Prognosis in this case must be guarded. The patient is still under observation.

SUMMARY

1. Sixteen patients with vasomotor rhinitis, some of them complicated with asthma, hay fever, and chronic sinusitis, who had obtained little or no relief from various other treatments, were given applications of pure carbolic acid to the nasal mucous membrane.

2. Phenol, when applied to the mucous membrane of the nose, blocks the nerve endings in the mucosa but does not induce desensitization.

3. The application is accompanied with little or no pain. The after-effects, which on the average last about two days, are headache, nasal obstruction, grippy feeling, and pain in the nose. In 2 cases there were occasional nose bleeds. Phenol leaves no scars nor is there any impairment to the sense of smell.

4. Of the 16 patients with vasomotor rhinitis so treated, 10 had complete and almost immediate relief from symptoms and 3 were moderately relieved. Of the 4 patients whose cases were complicated by pollen asthma, 3 were relieved of their asthmatic symptoms. The 2 patients with asthmatic bronchitis and 3 with vasomotor rhinitis were not relieved.

5. The application of pure carbolic acid to the nares relieves rhinorrhea, sneezing, and nasal obstruction in vasomotor rhinitis. The permanence of this relief is as yet uncertain. All the patients are still under observation.

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VACCINE THERAPY: THE USES AND MISUSES

A Statistical Bacteriologic Study*

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SINCE the introduction of vaccine therapy into medicine, the question of its value in the treatment of bronchial asthma has been the subject of much controversy. The actual status of vaccine therapy in general ranges today from utter condemnation by one class of internists to complete dependence by another class. Much has been offered to support both sets of claims. In the last six years we have been in a position to see the effects of impartial vaccine usage; a correlation of the mass of material gathered over that period from the allergic clinics of two Philadelphia hospitals combined with the private practice of Dr. Wilmer forms the basis of this statistical study.

Where the etiologic factor is as obscure as it may be in bronchial asthma, the so-called "gunshot" methods of diagnosis and treatment are frequently resorted to in the hope of effecting a cure, as well as a relief of symptoms. This is especially true in the use, indiscriminately, of vaccines, the usage of which has given a wide variation in results. This type of treatment is to be condemned as used at present. Allergists will protest loudly that vaccines are impractical and unscientific and still continue to use them as blindly as when they were first put on the market. Methods of dosage and types of vaccine therapy are still unstandardized and unscientific; and treatment is to be condemned in any form of biologic administration which is as unscientific, inaccurate, and undependable.

We hold no brief for vaccine usage; we do not believe in its specificity. Still we offer no substitute to take its place. Nor do we advocate any special type of therapy for bacterial asthma. The practitioner who regards each case as individual in diagnosis will get the best results if he treats each one with just as individualistic type of therapy. Whether stock vaccines, autogenous vaccines, soluble toxins, either alone or in combination with vaccines, or nonspecific proteins are used, there are good results reported by able men to substantiate each. From the experience and results of the series of cases observed by us, we feel that a nonspecific protein reaction is, in the majority of cases, the basis for success in vaccine therapy.

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BACTERIAL ASTHMA

Allergists, whether they use the scratch, intradermal, or ophthalmic methods of testing, divide sensitivity into the following groups: pollen sensitivity, animal epidermal sensitivity, food sensitivity, and sensitivity to unusual allergens of a miscellaneous sort, such as drugs, fungi, oils, etc. Patients not reacting to any of these groups of proteins are generally classified as being bacterial in type, and are so considered until proved otherwise. The frequent occurrence of continued and recurrent upper respiratory infections preceding or simultaneous with each asthmatic attack first established the bacterial connection. Acute coryza and influenza are very often followed by a recognizable bacterial hypersensitivity and patients repeatedly give histories of previously existing infections. In the series of cases from which this material is gathered, the patients are all classified as essential or idiopathic asthmatics of bacterial origin alone. Persons having a hypersensitivity to any of the other groups of proteins were eliminated.

It is important to determine the focus of infection in any case and to attempt to eradicate it, whether it be in the tonsils, teeth, sinuses, or the respiratory or gastrointestinal tracts. Local treatment with drugs, surgery, or bacteriophage has often done as much to clear up asthma permanently by the erradication of a focus as the use of quantities of vaccines.

To believe in the use of vaccines in the treatment of bronchial asthma, it is necessary to believe in the possibility of bacterial allergens being etiologic in asthma, or else that bacterial suspensions act as nonspecific proteins. Thus, results obtained by the use of vaccines are either due to the desensitization of this bacterial hypersensitivity or to an increased immunologic response, such as increased phagocytosis and antibody formation.

Assuming that a diagnosis of bacterial asthma has been made, the treatment with vaccine or supplemented vaccine therapy is what concerns us. The two methods of treatment which are generally followed and accepted at present are: (1) use of a stock vaccine as prepared by any good commercial biologic laboratory and which usually contains any number of strains of organisms common to the upper respiratory tract in normal and infectious conditions, and (2) use of an especially prepared autogenous vaccine from the site of infection, either tonsils, teeth, sinuses, or bronchi.

STOCK VACCINES

The use of stock vaccines has often given very satisfactory results, with a complete cessation of symptoms and frequently a permanent improvement. The use of a polyvalent streptococcus vaccine has been suc-

cessfully tried as well as the more common ones which combine all of the usual strains found in cultures from unlimited numbers of throats and sputa. Particularly in prophylaxis has there been an increasing trend in the last five years. Hicks,[1] reporting in England, states that the value of stock vaccine is not in treatment but in prophylaxis. We believe that good results, which are obtained by vaccines in general and by stock vaccines in particular, cannot be explained on any other basis than that of a foreign protein reaction.

Many allergists, contrary to Walker's[2] belief, feel that stock vaccines cannot lay claim to specificity any more than can autogenous vaccines. Variations in combining of stock vaccines have given as good results with unselected cases as with those in which a selected bacterin was used over an equally long period of time. In isolated cases, only on repeated culture have we been able to isolate a combination of organisms which effected a cure. In these unusual cases, specificity was definite. The use of B. *typhosus* vaccine intravenously has given as good results with fewer doses as the use of either polyvalent streptococcus vaccine or an influenza stock vaccine given intramuscularly, subcutaneously, or intracutaneously. The dosage in the use of a stock vaccine is extremely important in the result obtained and is dependent on the tolerance of the patient. Hence, no hard and fast rule can be established, but it must be individually regulated and controlled. Failure of any relief is primarily due to underdosage rather than to any one other specific cause. An insufficient number of bacteria per cubic centimeter gives insufficient stimulation to the reticuloendothelial system, just as insufficient aolan, leucocytic cream, or even HCl injections would do.

AUTOGENOUS VACCINES

The use of autogenous vaccines has had considerable vogue and is certainly on a more scientific basis. If carefully prepared by a trained bacteriologist or technician, no matter if the material used is sinus washings, sputum, or feces, the vaccine can be standardized more readily and adapted to fit the more individual requirements of the patient in regard to numbers or organisms, dilutions and strains included, which, obviously, is more scientific.

Allergists recommend in the preparation of autogenous vaccines that varying combinations of organisms will give better results. The preparation of all of the bacterins is essentially the same, the inclusion of the kinds and types of organisms being generally recommended in the following three ways: (1) the inclusion of *all* organisms cultured from the focus, whether they be normal inhabitants of the site of culture or not; i.e., a bacterin from sputum to include *Staphylococcus aureus,* pneumococci, diphtheroids, and *Micrococcus catarrhalis.* This type of

bacterin is most closely allied to the commercial stock vaccine and has very little more to recommend it other than a specificity of the strain of infecting or present organism. (2) An inclusion in the bacterin of only those organisms which are not normally present at the site of infection and which could be considered as pathogens for the case; i.e., if a sputum, when plated out, yielded *Staphylococcus aureus, Streptococcus hemolyticus I,* pneumococci, and *Micrococcus tetragenus,* the bacterin might contain *Staphylococcus aureus, Streptococcus hemolyticus I* and *Micrococcus tetragenus* or just *Streptococcus hemolyticus* and *Staphylococcus aureus.* (3) This is a selective method based on the skin reactions to isolated organisms and has been designated "pathogenic selectivity." The bacterin would include in proportion to the amount of reactivity of each of the bacteria, only such bacteria as give a definite reaction of 2-plus or more, the reaction of which persists for a period of from twenty-four to forty-eight hours. This method of vaccine preparation we have previously felt to be greatly overestimated and, in our results, we found that the percentage of cure and improvement was really higher than we had expected or observed. Even though the number of cases was small, it is to be tested further in the future. Control series in connection with the skin reactions gave practically negative reactions in normal persons, toxic reactions did not persist, and the tendency to false positives was considerably decreased. It appears to be on a much more scientific and dependable basis. If there is any justifiable claim for specificity, it is evidenced here.

In preparing five hundred bacterins by two different laboratories for use by three groups of workers, there are many factors which enter into the composition of the finished bacterin. Therefore, these have been kept separate according to the constituents of the vaccine and for comparative reasons are grouped accordingly. The methods of culture and isolation as well as of preparation were the same in technic; identification, however, was more complete from one laboratory than from the other from a bacteriologic standpoint.

In the first series, or P. group, the bacterins were prepared to include only those organisms present which could be considered pathogenic. The second group, or G. group, contained bacterins prepared by including *all* organisms present. After preparation, the suspension was shaken for twenty-four hours in a vaccine shaker with glass beads to break up the bacterial cell, the principle being that any endotoxins which might be present would be liberated on breaking the cell and so included in the solution and absorption would be easier than when absorption of the unbroken cell takes place.

The third or C. group used bacterins of organisms, containing both pathogens and normal inhabitants, which gave positive skin reactions.

The suspensions were shaken to include endotoxins. The normal organisms were included if reactions occurred, inasmuch as normal inhabitants could be extremely violent reactors, as shown by Dorst and Morris.[3] Detoxified vaccines were not included as recommended; where a toxin is present and not used, it is only using part of the material presented. It could be compared to a bacteriophage which had been chemically sterilized. Only gram-negative bacteria are successfully detoxified and in our hands these have been restricted to the colon-typhoid group. Gram-negative bacteria of the respiratory tract, such as *Micrococcus catarrhalis, Bacillus influenzae,* and the Friedlander group, do not detoxify successfully. We had no success with detoxifying any of the streptococci isolated, with the exception of *Streptococcus equinus,* and this was only partial detoxification.

With no previous correlation of success in vaccine therapy, no anticipation of the results could be made. In noting cures, all patients who had had no attack for the past two years were considered cured. Improvement was that stated by the patient. Results are set forth in Table I.

TABLE I

RESULT OF VACCINE THERAPY IN BRONCHIAL ASTHMA

	STOCK VACCINE	PATHOGENS ONLY "P" GROUP	ALL ORGANISMS "G" GROUP	SELECTIVITY "C" GROUP
Number of cases 150	44	27	64	15
Cured	14	9	16	4
	31.8%	33.3%	25.0%	28.0%
Improvement	22	13	30	9
	50.0%	48.5%	45.3%	60.0%
No Relief	8	5	18	2
	18.2%	18.9%	28.1%	13.0%

SUMMARY

Cured	43 cases	(28.6%)
Improved	74 cases	(49.3%)
No relief	33 cases	(22.0%)

This chart gives at a glance the results of the different types of bacterin therapy. In percentage, it can be seen that the selected organisms group is the highest. This may be explained on the basis of a low total number of cases. But in itself, it is noteworthy.

A comparison of the results obtained by stock vaccines alone as against autogenous vaccines for the 150 cases shows:

TABLE II

	AUTOGENOUS (106 CASES)	STOCK VACCINE (44 CASES)
Cured	27.3%	31.8%
Improved	49.0%	50.0%
No Relief	23.5%	18.2%

Voorsanger and Firestone[4] reported a series of 88 cases and in a comparison of their results with the use of autogenous vaccines as against stock vaccines they found:

TABLE III

	AUTOGENOUS (66 CASES)	STOCK VACCINE (22 CASES)
Cured	22.7%	32.0%
Improved	40.9%	36.0%
No Relief	36.4%	32.0%

Comparison of these results runs parallel to those found by us and tends to substantiate the claim of many observers, such as Rackemann[5] and others, that there seems to be little or no specificity in the use of autogenous vaccines. Auld[6] strikes the right note when he claims that protein shock is the basis for all successful vaccine usage. Both the German school, headed by Petow and Wittkower,[7] and the English school, by Oriel and Barber,[8] who used urinary proteose and peptones without consideration or even knowledge of a specific allergin, obtained good results with this nonspecific desensitization. Their use of tuberculin would correspond to the use of a vaccine, and the results are comparable with the results of our vaccine treatment. As seen in Tables II and III, there is slight variation in the results with the use of supposedly specific and nonspecific material.

SOLUBLE TOXINS

At intervals all of the group used a vaccine suspended in a menstruum which contained either a soluble exotoxin or an endotoxin. Supplementary therapy was frequently used, such as injections subcutaneously or intramuscularly with so-called secretion filtrates or soluble toxins. These are prepared in a protein-free media (usually Ushinsky's or a glucose-saline) by the method described and recommended by Wilmer,[10] and Eiman,[11] who reported the results in a series of 92 cases. Undoubtedly, the results and benefits described and obtained sufficiently justify the use of toxins. Our discussion is not concerned with the use of toxins, either soluble or insoluble; it deals with the unscientific use of a material the content of which we have no knowledge. As prepared, we do not even know if there is any toxin present; nor do we know what rôle it plays in cure, the mechanism involved or the reasons why; whether it has to do with antibody formation, phagocytosis or desensitization. We feel that a control series of cases should be (and will be) run to determine the reactions and results by using media alone, on allergic and nonallergic persons. For example, a control substance, such as asparagin could be used. This forms the basic supply for the

amino-group in Ushinsky's media. Standardization must be established and the fact that there is an increase in the nitrogen content of the cultured over the uncultured media cannot be accepted as a standard basis of toxin formation.

If a soluble toxin is produced by bacteria such as the staphylococci, to use a washed culture in vaccine preparation which excludes that toxin is to utilize only part of the natural characteristics of the organism. Shera[12] believes that where a bacterium forms an exotoxin, a serum is most desired; when an endotoxin is formed and liberated only on autolysis, a vaccine is more correctly indicated. Where both are present, the use of a serobacterin seems to us to be most rational.

An attempt was made to sensitize guinea pigs with soluble toxins. Two animals were used for each set of materials. These were given in increasing doses until a high degree of sensitivity could be assured. After a two weeks' rest interval on completion of the inoculations, 2 c.c. of the antigens were given intravenously and the results tabulated (Table IV).

TABLE IV

SET	ANTIGEN	RESULTS
I	Sol. toxin	Slight respiratory embarrassment, both pigs
II	Ushinsky's media	No change, either pig
III	Glucose saline media	No change, either pig
IV	Horse serum 1:1000	Complete anaphylaxis
V	Brain broth	Complete anaphylaxis

It is difficult to put an interpretation on these results with such a simple experiment, but it does raise very definite questions. Is the difference noted in the pigs injected with the soluble toxin media due to the slight sensitizing effect of autolysed bacteria, the presence of Besredka's virus, or the actual presence of some soluble toxin with mild atopic powers? In patients who sensitize themselves to their own secretions or to the bacteria and bacterial products they harbor, the allergic state which is evident in these patients is generally of such a pronounced character that we would expect animals sensitized to the same material to give more evidence of a sensitivity after inoculations with the soluble toxin material.

TABLE V

	EXOTOXINS	ENDOTOXINS	COMBINED TOXINS
Number of cases	23	56	8
Cured	30%	22.7%	33.3%
Improved	50%	45.2%	66.6%
No Relief	20%	32.0%	------

In 87 cases of bronchial asthma we were able to see the difference in the results by using just endo- and exotoxins (Table V).

The last column of 8 cases we feel is insufficient to add much to the conclusions. As in 4 other cases where no toxins were used, there was a 50 per cent cure and improvement. This also is too small a series to be other than coincidence.

BACTERIOLOGY

Richey[13] wrote, "The numerical method of research was given us by Louis and involves a careful analysis of facts accurately and impartially observed." The use of this system has given us clues leading to a better understanding of many obscure and impressionistic problems. Particularly is this true in the field of immunology and bacteriology. The careful interpretation of the results often clarifies impressions or corrects previously existing ideas.

From time to time there have appeared in the literature various reports of sputum cultures, tonsil cultures, and other cultures from the upper respiratory tracts of normal persons and asthmatic patients. In 1917 Koessler and Moody[14] made vaccines of both aerobic and anaerobic cultures of asthmatic sputa. Rackemann,[15] Thomas,[16] Walker[17] and others have all submitted reports from sputum cultures of asthmatic patients over a period of years. McKinney[18] recently reported a series of 50 cases having asthmatic bronchitis. This report contains at least in part patients with a diagnosis of true bacterial asthma and has a striking agreement with our observations.

The technic used by McKinney is essentially the same as ours. Only washed sputum was cultured and the plates streaked in a dilution-method pattern on blood agar. Incubation was from twenty-four to forty-eight hours at 37.5° C. Colonies were picked for subcultures and inoculated into other laboratory media, such as the sugars, litmus milk, broth, etc., for identification after isolation in pure culture. Streptococci were cultured in deep brain broth after they had been classified from the plates as belonging to the hemolytic, nonhemolytic or viridans group. Gram-positive diplococci were tested for bile solubility and when positive were grouped as pneumococci, no notation being made as to the type, or whether they were rough or smooth colonies. Practically all of the gram-positive diplococci which appeared to be pneumococci and were not bile soluble, when transplanted into Rosenow's brain broth, developed into short chain streptococci with definite fermentation of the sugars according to the classification of Holman.[19]

All in all, about 900 sputum cultures were made, but these were done at two different hospitals and the slight variations in technic and thoroughness of identification make a comparison of the two groups im-

possible. Where one group used the classification of streptococci according to Holman, the other group stopped with the reaction to blood agar and considered the fermentations unnecessary. Therefore, a group of only 500 cultures was studied. We feel, too, that the incidence of bacteria in the sputa of 500 asthmatic patients over a period of years gives several definite pictures and a clear, cross-section of the flora to be seen in patients showing an uncomplicated bacterial asthma. Table VI gives the incidence of organisms recovered.

We thought it important to determine just how many of these organisms which we recovered from asthmatic sputa appeared in the mouth

TABLE VI

INCIDENCE OF BACTERIA IN SPUTA OF 500 ASTHMATIC PATIENTS

	NO. OF CASES	PER CENT
Staphylococcus	143	28.6
albus	28	
aureus	115	
Micrococcus:		
catarrhalis	318	63.6
mucofaciens	1	
siccus	1	
tetragenous	80	16.0
Pneumococcus	312	62.4
Sarcinae	117	23.4
Bacillus	101	20.2
mucosus capsulatus	26	
influenzae	26	
coli group	9	
rhinosclermatis	32	
Diphtheroids	122	24.4
Streptococcus	337	67.4
mitis	48	
pyogenes	9	
ignavus	50	
anginosus	39	
subacidis	46	
equinus	9	
salivarius	80	
viridans	15	
hemolyticus I	12	
hemolyticus III	10	
nonhemolyticus I	12	
nonhemolyticus III	1	
faecalis	6	

NUMBER OF ORGANISMS ISOLATED PER SPUTUM CULTURE	
One organism	50 times
Two organisms	192 times
Three organisms	169 times
Four organisms	61 times
Five organisms	40 times
Six organisms	2 times
Seven organisms	2 times

flora of normal or nonallergic persons; that is, patients without any diagnosis of bacterial allergy. This is necessary for comparison. In Table VII, we have the incidence of bacteria from 200 patients from the surgical wards. These were patients admitted to the house without any complicating upper respiratory infections. We feel it is as nearly a normal cross-section as can be obtained for a group of this size.

TABLE VII

INCIDENCE OF BACTERIA IN THE CONTROL GROUP OF 200 PERSONS

	PER CENT
Staphylococcus	84.0
albus	18.0
aureus	66.0
Micrococcus	
catarrhalis	34.5
tetragenous	9.9
Pneumococcus	54.5
Gram-negative bacilli	24.0
mucosus capsulatus	14.0
influenzae	10.0
Diphtheroids	17.5
Streptococci	46.0
hemolyticus	30.0
nonhemolyticus	14.0
viridans	2.0

To compare the two tables the outstanding feature is the range in importance of the predominating organisms. The incidence seen at a glance is:

ASTHMATIC SPUTA		NORMAL SPUTA
Streptococci	1	Staphylococci
M. *catarrhalis*	2	Pneumococci
Pneumococci	3	Streptococci
Staphylococci	4	M. *catarrhalis*

The relationship of the streptococci is apparently similar to that found by McKinney[18] and others.

We know that the bacterial flora of the respiratory tract changes constantly and that the seasonal variations are noted in normal as well as in asthmatic persons. In classifying the incidence of the bacteria isolated in the 500 sputum cultures according to seasons, they were grouped. (Table IX.)

For arbitrary grouping the seasons were divided into Spring (March, April, May); Summer (June, July, August); Fall (September, October, November); Winter (December, January, February).

Nasal smears were made fram 222 patients whose site of infection was nasal or sinus and whose asthma was attributed to the existing infec-

TABLE IX

SEASONAL VARIATION OF BACTERIA IN SPUTA OF 500 ASTHMATIC PATIENTS

ORGANISMS	SPRING	SUMMER	FALL	WINTER
Streptococci	61	24	53	59
Staphylococci	24	19	29	32
Pneumococci	64	49	77	64
Diphtheroids	20	16	23	38
M. *catarrhalis*	57	49	56	73
Sarcinae	22	44	35	30

tion. These were cultured by the two hospital laboratories and the bacteria isolated. An average of the bacteria isolated in percentage is given in Table X.

TABLE X

INCIDENCE OF BACTERIA IN 222 NASAL CULTURES OF ASTHMATIC PATIENTS

	PER CENT
Staphylococci	27.9
Streptococci	15.9
Pneumococci	11.2
Diphtheroids	16.2
M. *catarrhalis*	8.3
Gram-neg. bacilli	6.3
THE NUMBER OF ORGANISMS ISOLATED PER NASAL CULTURE WAS:	
1 organism	isolated 64 times
2 organisms	isolated 67 times
3 organisms	isolated 36 times
4 organisms	isolated 5 times
5 organisms	isolated 1 time

SUMMARY

1. Each case of bronchial asthma of bacterial origin should be considered as an individual bacteriologic problem, particularly from the standpoint of treatment, and therapy should be adjusted to fit the individual case.

2. Bacterial allergy is a definite pathologic entity which responds to bacterin therapy, either through desensitization, increased phagocytosis, or stimulated antibody formation.

3. Stock vaccines as well as autogenous vaccines have little to recommend them unless they are regarded as effecting nonspecific protein reactions as shown by 150 unselected cases.

4. The use of a bacterin which includes all organisms isolated from the focus of infection has little more to recommend it than the use of stock vaccines, except in a small minority of cases.

5. Selective vaccines based on skin reactions give the best results and appear to be on a more scientific basis than other types of vaccines.

6. Soluble toxins as prepared and used by present technic have no scientific value unless controlled on nonallergic persons and unless standardized.

7. Experimentally, guinea pigs could not be appreciably sensitized with soluble toxin material.

8. Cultures of sputa from 500 asthmatic patients showed an incidence of bacteria in the following predominance: streptococci, M. *catarrhalis*, pneumococci and staphylococci. Sputa from 200 control persons showed the incidence to be staphylococci, pneumococci, streptococci and M. *catarrhalis*.

9. A series of nasal smears from 222 asthmatic patients showing nasal or sinus infections showed the incidence of bacteria to be in the following order: staphylococci, streptococci, diphtheroids and pneumococci.

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ASPIRIN ALLERGY

A Method of Testing for Aspirin Sensitiveness and a Method of Avoiding Aspirin Catastrophes

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ASPIRIN has gained a name of being a cardiac depressant. I doubt whether students of allergy so regard it, and I believe rather that aspirin illness is caused almost always by the taking of aspirin by aspirin-sensitive persons.

The effect of aspirin on aspirin-sensitive persons can amount to a catastrophe in every sense of the word. It can at a time within a few minutes to several hours or more precipitate an attack of allergy characterized by terrific asthma or hives, prostration, or shock symptoms which are sufficient to alarm any physician and which may resist the free use of adrenalin. The illness can last in great severity for several days or even one or two weeks or more. In one case reported by Cooke, death followed the taking of an aspirin tablet.

Aspirin sensitiveness is very common among allergic persons. Storm van Leeuwen,[1] from statistics, states that 10 per cent of asthmatic patients are sensitive to aspirin. Loudermilk stated to me that it is very peculiar how many allergic persons prove to be sensitive to drugs used in the symptomatic treatment of allergy. Very few aspirin-sensitive patients give positive skin tests to aspirin. Cooke,[2] who gave the first complete description of the drug allergies, states that he has observed only one positive skin test among his aspirin-sensitive patients. I have never yet observed a positive skin test in an aspirin-sensitive person.

Since at odd times one is inclined to use aspirin or aspirin with alcohol because of its definite benefit to certain asthmatic patients, the detection of aspirin sensitiveness in advance of administration is most important. I have several times used aspirin in asthmatic patients who had never taken aspirin and with anything but a desirable result. Before administering aspirin to an allergic person therefore, it should be a matter of routine to prove that the patient is not aspirin-sensitive. The physician can inquire about sensitiveness to the drug; in fact, for sensitiveness to salicylates in general. However, a great many asthmatic patients have never taken aspirin. It is surprising how often one encounters patients of this sort. One is then in a quandary as to whether or not to give aspirin if indicated.

I have devised a test for aspirin sensitiveness which is practical and quite definite. It depends upon the fact that aspirin is insoluble in

water and on this account is apparently not absorbable. In alkaline media however, such as saliva and intestinal juices, it is split into sodium acetate and sodium salicylate which is readily soluble and absorbable. It is for this reason I believe, that aspirin reactions are frequently delayed. The tablets as ordinarily taken are washed out of the mouth into the acid stomach juices and are not absorbed until they reach the alkaline intestinal juices.

The test is made by breaking off several small specks from an aspirin tablet and placing this on the patient's tongue and having him move it around in his mouth. In the case of a positive reaction a violent attack of cough, asthma, and itching may be precipitated within one minute. If the amount of aspirin which is administered is small in amount and not swallowed, the attack can be stopped within a minute or two by having the patient rinse his mouth repeatedly with a solution containing four cubic centimeters of dilute acetic acid or vinegar to a glass of water. This not only removes aspirin mechanically but stops its absorption. The use of adrenalin was unnecessary in my cases but could be used if indicated.

I have used this test and prevented almost certain catastrophes in three asthmatic patients who were violently sensitive to aspirin but who had never taken a dose of it. Also I have used aspirin with definite benefit in patients who had never used aspirin and who gave mouth-negative tests.

SUMMARY

A very simple test can be made for aspirin sensitiveness by placing a small granule of aspirin on a patient's tongue. In the case of a positive reaction, symptoms of allergy should appear within a few moments. In the case of a positive reaction aspirin can be removed and further absorption stopped by washing the mouth with a glassful of very dilute acetic acid. The symptoms produced could be controlled further by small doses of adrenalin if needed. The test should be tried in every allergic person before aspirin is administered, unless it is certain from history that the person tolerates aspirin well.

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Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

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Address of the President. ALBERT J. VANDER VEER, JR., NEW YORK, N. Y.

In surveying the field of allergy there are several points worthy of emphasis at the present time. Hypersensitiveness and endocrinology are the most recent subjects to enlist medical interest, and as in all newly discovered territories the rush for exploration carries with it not only the more sober-minded investigators but the hardy adventurous characters eager to see and report some new thing. We must make our observations more accurately than in the time-trodden fields of medicine, and our reports must be conservative, for the average general practitioner lacks the experience and special training to be able to separate the wheat from the chaff. We should weigh carefully our words and above all be sure of our conclusions before we put them forth in published articles. It is easy enough to gain notoriety by claiming new methods for the relief and cure of long-existing and intractable diseases. It is difficult or impossible to recall such claims when more careful study and experience have proved them overestimated or worthless.

On the other hand we have a duty to perform in giving wider knowledge to the facts and principles of diagnosis and treatment in allergic disease which long experience has shown us to be true and essential. Too many cases of hay fever, vasomotor rhinitis, recurring attacks of bronchitis, urticaria and migraine are still being treated without recourse to a thorough examination by a skilled allergist. Too many cases of asthma are labeled hopeless and incurable without competent nose and throat examination and treatment. We must combat the general attitude (which I confess seems to be gradually gaining ground) that allergy consists in scratching the skin with a few food tests and putting the patient on a weird and impracticable diet which usually accomplishes no result. We should be frank in admitting that skin tests are of little value where the clinical reaction is delayed but equally insistent that they be done where the clinical reaction is im-

mediate and we may expect them to be of the utmost importance. The reading of these tests and their interpretation should be done by a competent allergist.

Lastly, we should assert our importance in the modern field of preventive medicine. Ordinarily it is necessary to protect a dozen people that one may escape. In smallpox, diphtheria, tuberculosis, it is our aim to protect the entire population, but with us the field is narrowed to the relatively few. Our patients of tomorrow are the children of our patients of today, and it is therefore easier to plan our campaign of protection. We should impress upon our patients, tactfully and above all avoiding an alarmist attitude, that with early diagnosis and care their children can be saved from many of the ills from which they themselves have suffered. We know that half or two-thirds of the children of allergic individuals will eventually manifest some symptoms along the same lines, and at the first sign of undue upper respiratory, intestinal or skin disorder they should be studied by a competent allergist. In a normal child an occasional digestive upset, slight eczema, enlarged tonsils and adenoids or a rare headache may be matters of slight importance. In a child with a hypersensitive family history they may be the forerunners of serious and crippling illness, and this should be taken into account when a line of treatment is recommended.

To sum up, let us practice allergy with truth and honesty as to what we can and cannot do, with boldness as to what it is our right to attempt to do, and with foresightedness and vision to lessen the trials and preventable suffering of the future generation.

So-Called Urinary Proteose in Individuals Allergic to Ragweed. WARREN T. VAUGHAN, RICHMOND, VA. (For original article, see page 385.)

DISCUSSION

DR. LOUIS TUFT, PHILADELPHIA, PA.—I am very much interested in Dr. Vaughan's presentation because we have just completed a similar study on a group of 103 patients doing about 120 estimations. We used as a control, a group of nonallergic individuals and individuals with certain cardiorenal and other conditions in which allergy played no rôle. In addition to skin tests, we attempted a quantitative estimation by using a graduated centrifuge tube and, in a rough way, calculated the approximate amount of proteose that was thrown down. In the control group, using a percentage system, we found in 27 individuals, the amount of proteose averaged 0.22 per cent. In the cardiovascular renal cases, of which there were 18, the proteose was 0.64 per cent. In the asthmatic cases, of which there were 18, the proteose averaged 0.9 per cent which was not a great deal more than

the nonallergic cases. In 24 ragweed patients the average was 0.33 per cent irrespective of whether the proteose was obtained during the active period or during the inactive or quiescent period.

In the ragweed patients, again, we attempted to see whether there was any difference before the pollen season, during the season, and at the completion of the season. In 10 such patients studied, we found that duplicate examinations showed increase to a moderate degree in 6, a decrease in 3, and was stationary in 1.

Twelve asthmatic patients were skin tested. In none of these could we get a reaction above 1:100. We also obtained the same type of reaction to a proteose prepared from a nonallergic individual which we used as a control.

Thirty skin tests were made on the hay fever group; 19 were completely negative; in 11 there were no reactions beyond the 1:1000 dilution, and some of these gave a plus-minus or slight reaction, but there was a similar reaction in the control. We must conclude from these observations that while proteose is present and is eliminated in the urine of allergic individuals, it is also eliminated in the urine of nonallergic individuals and in particularly high concentrations in cardiovascular renal cases. As far as we could determine, there was no specific skin reaction.

DR. T. D. CUNNINGHAM, DENVER, COLO.—I am particularly interested in this paper because proteose was hailed as a cure in Denver. I tried out ten cases when this treatment first came out, with the results similar to those reported here, namely, that it does not work.

DR. MATTHEW WALZER, BROOKLYN, N. Y.—A point to be remembered in working on this type of case is that you can have a specific antigen excreted in the urine. In our work on absorption of unaltered protein we were able, on several occasions, to demonstrate the presence of an unaltered antigen in the urine. In other experimental work which we will eventually publish, we were able to demonstrate, following a subcutaneous injection of ragweed, that ragweed is excreted in the urine. This probably accounts for some of the positive skin reactions obtained with urine antigens which some authors report, but it is a far cry from what Barber and Oriel have suggested is the nature of their urinary proteose.

DR. HARRY LEE HUBER, CHICAGO, ILL.—Those who attended the meeting in New Orleans last year were surprised when the newspapers announced that many forms of blindness were due to allergic disease and that these were cured by using urinary proteose. A paper on this subject was read before the ophthalmological group, as allergists had not recognized the relationship.

Two years ago I investigated the so-called urinary proteose in proved cases of allergic disease. I succeeded in demonstrating it qualitatively in a few but did not find anything specific about it.

DR. W. T. VAUGHAN.—Oriel and Barber's first case, I think, was a case of serum sickness following the administration of horse serum. Of course, Rackemann and Longcope years ago showed that horse serum is excreted in the urine. One would expect to get a large amount of antigenic material in a case of serum sickness. I have no doubt that there are many others here who have investigated the so-called proteose and have discarded it. But since practically all that has appeared in the literature has been favorable to it, with the exception of the recent report by Trasoff and Meranze, it did seem to me that there should be something in the literature giving the results which it appears that most of us have obtained, because a number of people who have not made a study of it, ask about it and are under the impression that all of the work done on the proteose has yielded successful results.

The Treatment of Hay Fever and Pollen Asthma by Air-Conditioned Atmosphere. LESLIE N. GAY, BALTIMORE, MD. (Abstract.)

Through the kindness of the Frigidaire Division of General Motors the opportunity was afforded to study the effect of air-conditioned atmosphere on individuals suffering with symptoms of hay fever and pollen asthma.

A room large enough to accommodate four bed patients was equipped with a Frigidaire air-conditioning unit. The room had five windows, and a door which opened on the corridor of the Osler Clinic. These windows and the door were kept closed but not sealed; consequently outside air entered the room under the door, through the cracks of the windows, and through the door when it was opened during the routine care of patients.

PROBLEMS CONSIDERED

1. The air cleansing efficiency of the instrument from the standpoint of pollen and dust. (Determined by pollen survey.)

2. The effect which this room has on untreated hay fever subjects.

3. Observations on hospitalization of patients who suffer with hay fever and pollen asthma.

4. The effect of this room on individuals who spent the night in the air-conditioned atmosphere but during the day went into the outside air.

5. Control cases.

6. The treatment of individuals suffering with bacterial asthma in air-conditioned atmosphere.

SUMMARY AND CONCLUSIONS

The experiments in the treatment of pollen hay fever and asthma with air-conditioned atmosphere represent a new method of attack. The efficiency of the system used in the experiment has been demonstrated with most satisfactory results. The apparatus not only cools the atmosphere but cleanses it of dust and pollen grains. Even temperature and humidity were readily maintained throughout the period of experiment.

Complete relief was given to patients suffering with symptoms of hay fever, whether they occupied the room for several hours or for longer periods of time. Striking relief was given to patients suffering with pollen asthma within twelve hours after admission to the room. Control cases did not respond in a satisfactory manner; in fact by occupying this room the symptoms were increased. The relief of patients apparently depends not only upon the cooling of the atmosphere but also and chiefly upon the fact that the atmosphere is cleansed of the offending agents.

Unfortunately, when patients were discharged from the room to the outside atmosphere, their symptoms returned with equal severity. For economic reasons, therefore, in the average individual suffering with hay fever the method is as yet not satisfactory, but to those individuals who can afford to install such a system whether in their home or in their office, great relief can be offered.

DISCUSSION

DR. FRANCIS M. RACKEMANN, BOSTON, MASS.—I think it is quite worth while to have a carefully controlled experiment like this on record. To me the times during which symptoms developed and other times when they disappeared after contact was made and broken in this room are quite interesting and somewhat at variance with the old idea that if people could stay half their time in an air-conditioned room, they would remain free of hay fever all the time. Dr. Gay has shown that his patients develop hay fever, within fifteen minutes, on coming out of the room, and that they are relieved of hay fever within a few minutes, perhaps an hour or so after going back into the room. The relation between symptoms and environment is striking.

The methods of air conditioning are interesting. I should like to ask Dr. Gay about ventilation and whether because there was no provision for ventilating this room with new air, it was simply a question of cleansing the air already there. I would ask him if the patients were entirely comfortable from that point of view.

The second thing I would like to bring out is the marked variation in the actual grams of water per cubic meter of air in accordance with the changes in temperature. Those differences are quite marked, and

to bring that out, I would ask Dr. Gay if he would give us a little idea as to how much water was removed from the air of this room in any given period.

DR. W. T. VAUGHAN, RICHMOND, VA.—We also have been working with an air conditioner. Our experience is comparable to Dr. Gay's. There are one or two points that might be interesting to bring out. Our total pollen count for the entire season on the windowsill outside of an adjacent room for the period of observation was about 6,300. The total count in the adjacent room for the same period was about 1,500. The total count for the conditioned room was 6. We introduced an estimated 200,000,000 pollen grains into the intake of the machine and about 18,000 passed through, most of them being collected on the coils of the machine. We introduced 15 grams, a tremendous amount, of lycopodium spores into the room, and in a period of three days one gram was obtained in the condensation water. Of course, it is obvious that some settled out and the machine could not pick it up off the floor and carry it to the machine. We then introduced approximately one billion grains of ragweed into the room; kept the air of the room circulating with fans; made counts of the room daily, counts of the exhaust air from the machine, and counts of the pollen settling on the floor. It took about a month for all of the ragweed and lycopodium to disappear from the room.

We are now building a closed circuit machine with a wind tunnel connecting the intake and the exhaust, with the idea of determining, if possible, whether all of the pollen is completely removed and in how long a period, and how many times it has to recirculate.

We were not very fortunate in putting patients in the room because it was in a private hospital and the cost of hospitalization entered in. We have only had two patients, one of whom was also sensitive to feathers. Through inadvertence she forgot to bring her pillow, slept on a feather pillow and was not relieved. She only spent one night there.

The other was a patient with very severe hay fever with a great deal of edema of the nasal mucosa. The nose was swollen tight shut. In twenty-four hours she was 25 per cent relieved; in forty-eight hours, 50 per cent relieved. She had had no previous treatment. In three days, she was 75 per cent relieved. She then left the room, remained symptom free for about two days and a half, during which time the atmospheric pollen count was rather high, and then symptoms returned and we proceeded with coseasonal treatment, again obtaining about 75 per cent relief. So that the relief obtained in the conditioned room was about the same as that obtained with coseasonal desensitization.

DR. HORACE S. BALDWIN, NEW YORK, N. Y.—I should like to ask Dr. Gay what he thinks of the importance of humidity-controlled atmosphere for the perennial asthmatic patients.

DR. MILTON B. COHEN, CLEVELAND, OHIO.—I am very much interested in this air-conditioning apparatus. It is a very marked improvement over any type of filter which merely takes out the pollen, particularly in the hot summer days. Any machine which will throw the pollen out, gives a certain amount of relief to the patients, but they suffer also because of the high relative humidity. All of these machines which, like the Frigidaire, depend upon the precipitation of moisture, and the washing out of the materials by cooling, naturally require a certain time period to get out the floating material. It is not to be expected that merely passing air over a coil once will take out of it all particles of matter that are in the air.

The machine should work quite satisfactory. We worked with a number of experimental air conditioners, using this principle: The colder you have your coils, that is, the greater the difference between the temperature of the coil and the temperature of the air, the greater the efficiency during that particular passage over the coil because the more water is thrown out at that time. With this type of apparatus, we do not have to worry about ventilation, because the mere cooling effect of the air causes sufficient intake of air from the unsealed windows and doors to get an adequate oxygen supply. Of course, you are bringing in pollen and dust-containing material which ultimately get recirculated through the machine and filtered out.

My experience with the handling of patients has not been quite as dramatic as Dr. Gay's, either in the time necessary to obtain the relief, or the rapidity with which symptoms recur. We have seen individuals who have relatively mild symptoms clear up in a few hours' time, but our experience has been somewhat more like the experience of Dr. Vaughan with his patients, that there are many of them who have a considerable lag before they obtain relief. These are in rooms where the humidity is not controlled. Whether that makes any difference and explains the difference between Dr. Gay's results and ours, I do not know.

Also, we have had quite a number of patients who are able to be out in wards and even outside for longer periods than Dr. Gay reported. Perhaps some of them had mild symptoms and, as far as they were concerned, felt so much better than they had previously that they would report that they were well. Of course, you would not expect a patient to be able to be in a high ragweed-containing atmosphere very long without having severe symptoms.

There is one other thing I think we as specialists should think about and that is that almost every day or two some one walks into our office with some kind of a fan under his arm and says, "Doctor, here is a thing I want to sell to all your hay fever patients." There are some fifteen or twenty different fans, holding anywhere from a quart

to a gallon or two of water, and a belt that goes around. I think most of you have seen them; they are designed to recirculate and cool the air. These things will take out very little pollen because the water cannot be kept cool enough to do the job. If you are going to air condition, air condition with something that is efficient. These other things are worthless.

DR. S. S. LEOPOLD, PHILADELPHIA, PA.—Nine years ago, in 1924, my brother, an engineer, and I equipped an air-conditioned room in the University Hospital in Philadelphia, using a commercial air washing machine. The air was passed through a water spray and through certain gross filters. That room, some of you will recall, was equipped with automatically recording wet and dry bulb Tycos thermometers, and the air was kept cool by feeding ice into the machine. Some of this work was done during the winter by using the ordinary heating apparatus in the room. We were able to draw certain conclusions: certain types of allergic asthmatic individuals were completely comfortable in the room and promptly had recurrence of symptoms in the adjoining ward; those who had bacterial infections, particularly multiple sinus disease, were not relieved to any extent, despite an effort to control the relative humidity.

We thought the room had a diagnostic importance because patients with dust asthma were immediately thrown into a paroxysm when dust was artificially introduced and were relieved in a relatively short time after the air had been cleaned. We drew deductions about the presence or absence of the mechanical factor by introducing in the case of one patient who was dust sensitive, a tremendous amount of inert material, animal charcoal, which caused no reaction whatsoever. All of these studies were published in the *Journal of the American Medical Association* in 1925.

I think this work is fundamentally important. It is much too costly for ordinary use. Our little experiment involved an equipment costing $500. I think it would be better for all of us if more careful studies were made along the lines which Dr. Milton Cohen previously followed regarding the efficacy of the inexpensive air filters which patients can afford to buy and install.

DR. M. B. SULZBERGER, NEW YORK CITY.—These experiments with Storm van Leeuwen's allergen-free chambers and with air-conditioned rooms, that is, with compartments in which patients can be kept and in which there is a relatively low dust and pollen content, and so forth, are interesting to the dermatologist also. A certain percentage of the skin diseases associated with infantile eczema, i.e., disseminated neurodermites, papular urticarias and prurigo mitis (you are going to hear Drs. A. Walzer and Grolnick's paper on this group

this afternoon), are not generally caused by direct contact with the substance by the skin, but by hematogenous distribution after absorption through the digestive apparatus, as in the case of foods, and, *perhaps equally or even more important, also by contact of the skin with an excitant which has been inhaled.* I think that absorption through the lungs and dissemination through the blood stream to the skin are illustrated quite well in the cases of some disseminated neurodermatites which were sensitive to silk. These patients knew that they could not stand silk on their person nor silk in their vicinity, that each time they had an intimate contact with silk (some had to keep silk out of their rooms, as far away from them as possible), there was an exacerbation of their skin eruption. However, when one tested their skins by means of applying silk to the skin, by means of patch test, there was no reaction, i.e., there was no contact dermatitis to be elicited by the contact with silk. It was, therefore, logical that there must have been some other means of entry into the skin and to the superficial vascular apparatus. These patients gave maximal positive reactions to silk when they were tested by means of intradermal testing. They also had reagins to silk.

Before we can say that skin tests (wheal reactions) are of no clinical significance in this group, we must consider the elimination of all substances which are possible etiologic agents in some of these atopic eruptions, as I shall call this group. *Among these we must include the air-borne excitants which enter through the respiratory apparatus.* I have been contemplating experiments along these lines, and have been putting cases of skin eruptions of this group not only on elimination diets but also into relatively allergen-free or excitant-free chambers.

I should like to ask Dr. Gay one question. My experience in air conditioning is limited to skin diseases. I have used the allergen-free rooms, and the type of room used in experimental work with oxygen. In these latter the air is very highly purified. The air in some of these rooms is so freed of impurities that a blood plate put before the entrance pipe will, after an exposure of one day, sometimes show not one colony of bacteria and sometimes only one or two colonies.

My experience is that when the patients are relieved in these chambers (as they often are) and are then put into the outside world and have renewed contact with the excitant, not only do their symptoms return but they often do so in an aggravated manner. It is as though during the time that they have been getting continual contact, a certain degree of desensitization was continually taking place and when this contact is stopped for a while, their sensitivity rises. I should like to know whether that coincides with Dr. Gay's experience.

DR. LESLIE N. GAY.—Dr. Cohen has answered Dr. Rackemann's question regarding ventilation. The amount of air which comes into this room is sufficient to replace air which might be considered stale.

With regard to the water precipitation, this of course depends upon the humidity of the outside air which comes into the room through the cracks and through the open door. In a period of twenty-four hours the amount of precipitation which was obtained from a room large enough to accommodate four bed patients, was in the neighborhood of a gallon of water. A half-gallon drip pan under the instrument was emptied twice in twenty-four hours.

Dr. Vaughan mentions that he has had some experience with hay fever and air-conditioned atmosphere. He says that he has tried this method of treatment in only two patients. In the experiments which I have just reported, at least sixty patients were under observation.

Thus far no attempt has been made to study asthma caused by the inhalants, such as dusts, orris root, feathers and animal danders, and, therefore, I can give you no results in the treatment of such individuals.

The question of expense is, of course, of interest, and it is this factor which restricts the use of the apparatus. Until a convenient portable machine is on the market, the average individual can hardly afford to install it in his home or office.

No bacterial studies as yet have been made of the cooled air as it leaves the instrument.

Studies in Atopic Hypersensitiveness of the Ophthalmic Mucous Membranes. H. SHERMAN, L. FELDMAN, AND M. WALZER, BROOKLYN, N. Y. (Abstract.)

A series of investigations upon hypersensitiveness of the ophthalmic mucous membranes in human beings revealed the following findings:

1. The ophthalmic mucous membranes may be passively sensitized with human serum without difficulty. This was accomplished in 17 successive cases; in 12 instances with a ragweed serum, and in 5 with a rabbit epithelium serum. Such passive sensitization was shown to persist for at least one to five weeks. The technic of sensitization is similar in principle to that employed by Prausnitz-Küstner for passive sensitization of the skin. Following the instillation of a few drops of 2 per cent butyn solution, 0.1 c.c. of the sensitizing serum was injected into the ocular conjunctiva. Tests for hypersensitiveness were performed two to ten days later by the usual ophthalmic test technic.

2. Following an initial reaction of the ophthalmic mucous membrane, partial refractoriness to further reaction exists. This was demonstrated in 38 out of 45 pollen sensitive cases. Such refractoriness is

nonspecific in character and may persist for four weeks or longer. This property of mucous membrane is similar to that manifested by the skin after trauma or whealing.

3. By means of the Zeiss Slitlamp, the ophthalmic reaction in the atopic individual was studied under magnification and compared with the reaction in the passively sensitized conjunctiva of a nonatopic individual. The reactions were found to be similar in every respect. The specific pollen reaction and a nonspecific one produced by a 0.25 to 1 per cent solution of dionin were then compared. They were found to be very similar except that in the latter there were fewer vessels injected, and the edema of the tissues was more marked. The positive ophthalmic reaction in atopic hypersensitiveness is primarily characterized by vascular dilatation and edema. No evidences of muscular constriction could be noted at any time.

DISCUSSION

DR. A. F. COCA, PEARL RIVER, N. Y.—I was most interested in the authors' failing to observe any contraction of the vascular muscular tissue in the course of the reaction at any time. This can be taken as throwing considerable doubt on the assumption that has been pretty general that the atopic reaction in asthma is essentially and primarily a muscular one.

One could say that the vascular muscular tissue is different from the bronchial muscle, that whereas the bronchial muscle may contract, the vascular unstriped muscle need not. Against this we have the demonstration by Ella F. Grove that in the rabbit and the guinea pig, especially in the guinea pig, all unstriped muscle, whether in the bronchus, in the vessel, or elsewhere, reacts under the specific stimulation of the antibody antigen reaction—this in spite of the fact that in the guinea pig there is no obstruction of the vascular system, as in the rabbit. The difference there is simply an anatomical one. The unstriped muscle in all situations in anaphylactic shock contracts but it happens that in the guinea pig the contraction of the arterial media is not sufficient to interfere with circulation; whereas, on the other hand, the contraction of the bronchial muscles in the rabbit does not cause an interference with respiration as it does in the guinea pig.

This observation of these men we have just heard certainly puts the burden of proof on those who consider that the asthmatic attack is due primarily to a muscular contraction.

DR. SALVATORE J. PARLATO, BUFFALO, N. Y.—I feel that the presentation of this paper has opened up a new field of endeavor for the allergist. Its value has been brought to my attention very forcibly in the last four or five months. We all see cases of hay fever, whether

perennial or seasonal, in which there is a decided conjunctivitis. I do not mean the typical reaction in which there is simply an injection of the vessels and edema, but I mean a secondary so-called inflammatory or bacterial conjunctivitis. The same condition may be compared to the secondary ethmoiditis in the nose.

Late in December of last year, an ophthalmologist referred a case of corneal ulcer to me. Somewhere he got the idea that this case was refractory to ordinary treatments given by ophthalmologists because of some other underlying and heretofore unknown reason.

The patient was a young man twenty-two years of age who had had corneal ulcers for four years, with frequent exacerbations and itching and redness of the conjunctiva. Besides the symptoms, there were frequent head colds which on close questioning might be interpreted as allergic rhinitis or perennial hay fever. At any rate, the young man had been receiving treatments over a period of four years not only by the ophthalmologist but by a nose and throat man, without any results.

The family history was negative, personal history negative, outside of the fact that he needed nose and throat treatments. Examination showed an ethmoiditis on the right side. The x-ray examinations of the sinuses and lungs were negative. The skin tests revealed reactivity to feathers and several foods.

The man was studied in December, and on elimination of foods from his diet and elimination of the feathers, the eye doctor reported to me that in the following four months there was no recurrence of the symptoms in the eye.

I do not wish to report this as a case that really should call for any particular comment, but merely as a preliminary report and perhaps to interest us more in the possibilities of handling these chronic conditions of the eye as well as the chronic conditions of the nose from an allergic point of view.

The cornea lends itself very well to lesions such as ulcers. We know that the cornea's superficial layer is made up of stratified and columnar epithelium, and it is easy to conceive where an allergen is introduced into the eye, particularly if air borne, it could start the itching and the accompanying rubbing of the eye actually abrade and damage the epithelium. Then it is very easy thereafter for bacteria and for further irritation caused by contact to keep up this irritation and lead into the formation of ulcer.

I wish to express my appreciation also of this very fundamental paper which we have heard this morning.

DR. A. H. W. CAULFEILD, TORONTO.—I should like to ask two questions in regard to this work. It was mentioned in the paper that

the reaction was easily controlled by adrenalin. Has Dr. Sherman observed that it is sufficiently true that one can do these tests on the patient without much fear of his strenuous objection—or without danger to the patient?

The second question is, have they done any work experimentally with animals? I ask that because at the particular time we have reinterested ourselves in passive transfer and sensitization in animals (to pollen extracts). We are able to demonstrate this experimentally as any one can. A little while ago, we tried in a series of animals (that were known to be sensitive) instilling the antigen in the eye, and much to our regret, we could get no reaction in the eye of the animals, although we could prove they were sensitive by hypodermic injections or the uterine horn method.

DR. M. B. SULZBERGER, NEW YORK CITY.—One of the main questions here is whether, in the passive transference to mucous membranes, we have a method which is more sensitive than the usual Prausnitz-Küstner transfer. We may then be able to pick up cases that were positive on direct testing or which should have been positive on clinical evidence, which do not show passive transference of antibodies when tested by the Prausnitz-Küstner method. The serum may still be able to sensitize the conjunctiva.

One of the interesting points in these results is that of nonspecific causation of a refractory period. This corresponds almost entirely with the findings in Jadassohn's Clinic about twenty years ago, and more recently verified and enlarged by Chen, working with primary whealing substances—morphine, atropine, pilocarpine and histamine. Chen found that in dogs these substances produce wheals. By repeatedly injecting a certain site with small amounts of these primary whealing substances, this site would become exhausted and become refractory.

There is one slight difference between their results and Walzer's. They found that one could exhaust a site with one substance so that it would no longer react to the same substance. But when a new excitant or new primary whealing substance was applied, Chen found it still caused a slight wheal.

Another interesting point is the similarity in the reaction of sensitization, that is, one in which an atopic excitant is brought into the conjunctiva and that which occurs when a primary irritating substance is brought into the conjunctiva. This coincides with skin work which has been done by W. Jadassohn in Zürich, in which he compared the reactions elicited in skins, first, by injecting an atopic excitant in an atopic skin; second, by injecting an atopic excitant in a passively sensitized skin; and, third, by injecting primary whealing

substances, such as morphine, histamine, pilocarpine, atropine, and codeine, I believe, into nonallergic, nonatopic individuals. All of these reactions *were essentially the same histologically.* They all showed eosinophiles. That is a most important point. In the skin, at least, *eosinophiles can no longer be considered to be characteristic of an atopic or allergic reaction,* but are probably simply pathognomonic of a wheal or of any rapid exudative response.

It seems probable that this may also hold true of rhinorrheas, etc., and we may perhaps be wrong in considering the presence of eosinophiles as evidence of allergy. Their presence is *certainly not evidence of atopy* (intestinal parasites, dermatitis herpetiformis, etc.).

DR. MILTON B. COHEN, CLEVELAND.—The thing that interests me is that the examination by means of the lamp of these two types of reactions, the nonspecific dionin reaction and the specific ragweed or timothy reaction, confirms work which we did histologically in the study of the atopic and the nonspecific reaction in the same individual, more of which we shall discuss this afternoon in our paper.

Histologically, the reaction produced in the atopic individual by histamine, morphine, codeine, or any of these nonspecific agents, is indistinguishable at the same period of time, whether it be thirty minutes, an hour, an hour and a half, from the reaction produced by the specific material. It is not the same histologically in the individual who is not atopically sensitive. If you put histamine into an atopic skin, you get a wheal indistinguishable from a wheal in a sensitive individual. If you remove the wheal and examine it histologically, you will find there is a minimal reaction in the non-sensitive individual histologically; I am not speaking of the surface wheal which you can see. Even after the surface wheal is gone, there is a minimal reaction in the skin of the non-sensitive individual, and there is a very distinct reaction lasting a long time in the sensitive individual.

It interested me, therefore, to find that by another method of study the nonspecific reaction and the specific reaction in the sensitive individual are indistinguishable. I think this type of controlled experiment is the type of work that men in this Society should do.

DR. J. A. CLARKE, JR., PHILADELPHIA, PA.—I should like to ask why, if there is a refractory period in the conjunctiva, a hay fever sufferer can have eye symptoms continuously for days or weeks at a time.

DR. M. WALZER, BROOKLYN, N. Y.—Dr. Coca's discussion on whether the primary mechanism of an atopic reaction is edema or muscular spasm has been a point of great interest to me. I was subjected to much criticism last year by the critics of my discussion on

asthma when they said that it seemed unreasonable for me to take the stand that asthma was caused by edema, in view of the fact that almost everybody believed that it was primarily a condition of muscular contraction and muscular spasm. It seems significant that our experiments in the wheal formation showed no evidences of muscular spasm and that our experiments on the atopic reaction of the mucous membranes do not show any evidences of muscular spasm. I think Dr. Coca expressed it correctly when he said the burden of proof now should be with those who are exponents of the muscular spasm theory to prove to us that there is any primary atopic reaction in the smooth muscle in humans.

In regard to Dr. Caulfeild's question concerning the possible danger or the harm in this technic, I might say that it is rather a delicate procedure. I do not think that it will ever get to the stage where it will be of practical diagnostic importance, but it is a perfectly safe experimental procedure if you filter the serum and work carefully. We have had absolutely no trouble so far. Adrenalin controls the reaction very well, and if one administration does not, a second will.

In regard to animal experimentation, we have done none because we are working with the human atopic reagin, and thus far I am not convinced that anybody has shown any passive sensitization of animals with that antibody.

In regard to the question of the identity of the histamine reaction and the atopic reaction, that was Lewis' original contention, and we have, until recently, been inclined to accept his idea. Our next publication in this series, however, will show one decided difference between the physiologic response of tissues to histamine and to a specific antigen which may raise considerable question as to the correctness of Lewis' view.

In reply to Dr. Clarke's question as to why patients who are having hay fever continuously, do not have refractory periods, I may state that if you watch for them, you will find periods of partial refractoriness in these cases. You will notice it particularly after a constitutional reaction. As a matter of fact, some men try to get constitutional reactions. I do not endorse that policy, but they try to get constitutional reactions on the ground that the patient feels better after them. This improvement is not due to desensitization, as I have previously pointed out, but probably to a refractory state of the mucous membranes.

In regard to the question Dr. Sulzberger asked, concerning refractoriness being nonspecific, I wish to bring out the fact that Dr. Cooke demonstrated this originally when he repeatedly stimulated the skin with one atopen and was able to show practically complete exhaustion

of the site to other atopens. This was done to disprove Mackenzie's original idea that he was working with a specific desensitization.

The Effect of Consecutive Years of Treatment Upon Cutaneous Sensitiveness in Late Hay Fever. HARRY MARKOW AND W. C. SPAIN, NEW YORK, N. Y. (For original article, see page 363.)

DISCUSSION

DR. A. VANDER VEER, NEW YORK CITY.—Dr. Spain asked me to check up on some of the cases of hay fever we have treated to see whether our figures corresponded with his. I reviewed 20 cases we started treating in 1928 and had treated consecutively for five years. In 1928, of these 20 cases, 5 came under class A, 14 under class B, and 1 under class C. In 1930, two years later, there were no cases in class A; there were 14 in class B and 6 in class C. In 1932, there were no cases in class A, 12 in class B, 7 in class C and 1 absolutely negative. In other words, 13 of the 20 cases were less sensitive in 1932 than 1928, 6 showed the same reaction and there was 1 case which apparently was more sensitive in 1932 than in 1928. Of course, the decrease in sensitiveness was not regular from year to year. One year they might be a little more sensitive and the next a little less, but in general they were less sensitive. Last year I tried testing some patients before the season began and after they had had a full season of treatment. I began with 20 or 30 cases, using both scratch and intradermal methods, to see if there would be any change in the reactions such as Dr. Colmes had reported. While I started with 20 or 30 cases, I was able to follow only 9 to the end of the season. Of these, none showed any change in sensitiveness by intradermal tests, while three were slightly less sensitive by the scratch method. None of them became absolutely negative.

DR. FRANCIS M. RACKEMANN, BOSTON, MASS.—During this year, Dr. Colmes and I have been much interested in the changes in skin tests, and I think we have solved our difficulties to some extent by finding that the changes are dependent upon differences in technic.

There are three items in technic. The first is the item of treatment; how much treatment and how long-continued treatment. One series of patients we had was treated only during the season, and from year to year we did not think that the tests in those patients changed, whereas another series of patients was treated at intervals through the year, and in them it was possible to show a definite change.

The second item of technic concerns the method of skin tests, and we find that the intradermal method does not show much change. The scratch method, however, using serial dilutions, does show a significant change in many of the cases.

The third feature of technic concerns the recording of the results. I am always skeptical of conclusions which are drawn from any written statement of "three plus" and "two plus" results. Since I left Dr. Longcope, all tests in our clinic have been recorded by making actual drawings and then measuring the reactions with a millimeter ruler. So today we still have a graphic picture of the tests that were done ten or fifteen years ago, and we know where we stand as far as the size of skin tests goes.

DR. HARRY LEE HUBER, CHICAGO, ILL.—I want to ask also about the method of recording. For eight years I have been testing patients at the beginning of the season and then at the close of the season. I use dry pollens exclusively by the scratch test and have made graphic records of these skin tests over this period.

I compare the skin tests at the beginning of the season with those that are made with the same pollens at the close of the season. I make a graphic drawing of the wheal after a given time and also a drawing of the zone of erythema around it. In 75 per cent of the cases there is a distinct decrease in the reaction from year to year.

However, the clinical results and the decrease in skin tests do not always agree. A patient may have fair clinical results and have no decrease in skin reaction, and a few may have marked decrease in size of reaction with unsatisfactory clinical results.

I think it is of value to have such records so that one can make comparisons at any time.

DR. HARRY L. ALEXANDER, ST. LOUIS, MO.—I think there is not quite sufficient accuracy in making comparisons of drawings of positive skin reactions. I should like to suggest a more precise method of measurement, namely, the use of a perimeter. This is a very simple instrument that will record directly in square centimeters the area of the wheal.

DR. T. D. CUNNINGHAM, DENVER, COLO.—There is another factor and that is the condition of the patient at the time the test is made. For instance, an asthmatic patient comes in, and you try the skin test by the scratch method. And the control reacts immediately, so you feel it is hardly worth while that day. A dose of calomel and salts and no breakfast will cause this same patient's skin to react in a normal manner to the scratches. This is not true of all patients but it is true of a certain percentage. I think the general condition of the patient at the time of the tests is a factor to be considered.

DR. GEORGE L. WALDBOTT, DETROIT, MICH.—I have observed that the results of skin tests are different at the time when no pollen is in the air than during the pollen season. Even in fall hay fever pa-

tients who are potentially sensitive to timothy, inasmuch as they give positive tests to timothy but do not show clinical sensitivity, the reactions to ragweed were stronger during the time when timothy was in the air.

DR. HARRY MARKOW.—Since reports have appeared describing the changes in cutaneous sensitiveness in a given season, and, since so many men were at variance with these reports, in so far as one group used the cutaneous method of testing and another group used the intradermal method, we decided to see whether we could find any such reduction in skin sensitiveness in a given season, and, if not, over a period of years. Our first procedure was to test our patients at intervals during the season.

In testing our patients, we classify them according to their reactions to the dilutions of ragweed extract containing 0.0001, 0.001 and 0.01 milligrams of N per cubic centimeter. Depending upon the reactions to these dilutions, they are classified into classes A, B, or C. A case is tested and, before any treatment is begun, is retested the following week. If there is any difference in the readings, the patient is retested again, and, if necessary, again, so that a definite classification of that patient is made. It is very difficult to put these tests into graphic form, and in tracing wheals of so-called marked reactions on paper, we find that they do not seem marked nor do they appear the same as they do on the skin. Also, the rapidity of whealing, the erythema, the accompanying itching and other factors that must be taken into consideration in making a classification do not appear on a graph.

In going over the charts for the last five years, we have found the lessening of skin sensitiveness, as shown in graphic form on the slides, to be present. These patients as a group have shown a definite diminution in skin sensitiveness. I am interested to learn that Dr. Vander Veer has noted similar results in his cases.

In testing by the intradermic method, we try to inject the same quantity of extract for each test. That is, of course, a difficult problem with the syringes that we are now using. However, I feel that the quantity of extract used in testing is not of importance, especially when dealing with marked reactions. Recent tests on ragweed sensitive cases have shown that the marked reactions appeared with varying amounts of extract injected.

On the Plan of Standardization of Pollen Extracts Proposed by Cooke and Stull. ARTHUR F. COCA, NEW YORK, N. Y. (For original article, see page 354.)

DISCUSSION

DR. ARTHUR STULL, NEW YORK CITY.—It is of fundamental importance to obtain an understanding of the chemical nature of the

pollen allergen in order to arrive at a sound method for accurate standardization of pollen extracts. We have suggested the protein nitrogen content of pollen extracts as a more accurate measure of their activity, since the weight of experimental evidence indicated that the active material was protein. This was based on rather extensive chemical and clinical studies.

Dr. Coca concluded from the failure to inactivate ragweed and timothy pollen extracts by three- to six-day digestion with pangestine that the pollen allergen was nonprotein in nature. All proteins, particularly vegetable proteins, vary in their digestibility by proteolytic enzymes, and the specificity of enzyme action is well known. The failure to inactivate pollen extract by pangestine does not necessarily indicate the nonprotein nature of pollen activity. As a matter of fact, Bouillenne and Bouillenne in 1931 in the *Bulletin of the Belgian Royal Academy* showed that ragweed pollen extract although resistant to proteolytic enzymes, was reduced in ten days and inactivated after fifty days' digestion with pangestine. Similarly Loeb in the *Biochemische Zeitschrift* in 1930 showed that foxtail and orchard grass extracts were inactivated by proteolytic enzymes and concluded that the active principle was protein or a substance active only in combination with protein. These positive results contradicting the findings of Coca and Grove indicated the protein nature of pollen activity. Jacoby in 1901 concluded from the failure to inactivate ricin by tryptic digestion that its activity was nonprotein in nature, but Osborne, Mendel and Harris subsequently showed that the toxic properties were only associated with the water soluble protein separated from the castor bean, that the toxicity was proportional to the amount of albumin, that the reactions, chemical composition and properties were characteristic of protein, and no evidence was obtained that their purified ricin contained more than the most insignificant trace of any other substance.

The experimental results reported by Coca and Grove in 1925 do not prove the nonprotein nature of pollen activity. The material within the collodion membrane showing activity contained nitrogen. It was not correct to conclude from a comparison of the nitrogen content in two different collodion membranes that in the one the pangestine had been quantitatively retained while in the other the pollen protein had been completely digested, leaving the pangestine quantitatively behind. Collodion membranes are only a qualitative means of separating material of protein nature from easily dialyzable material of small molecular dimensions. The degree of membrane permeability depends upon the thickness and upon the length of time the sac has

dried previous to the addition of water. Small amounts of protein will dialyze depending upon the nature of the particular protein and the permeability of the particular membrane, it being practically impossible to prepare two membranes functioning quantitatively alike. General textbooks on biochemical methods illustrate the dialyzability of egg albumen through the ordinary collodion membrane and suggest the use of a hardened membrane in order to reduce this loss.

The failure to demonstrate the presence of nitrogen or protein in solutions showing activity is not evidence against the protein nature of the active material. Our pure pollen protein solutions containing from 1:10,000 to 1:100,000 mg. of protein nitrogen per cubic centimeter, this concentration having been arrived at by dilution of concentrated solutions, gave marked reactions in sensitive cases. It is impossible chemically to determine the nitrogen or protein in such high dilution, but physiologic tests show activity, since they are much more delicate than chemical tests for protein.

Northrop had shown that solutions of pepsin and trypsin in dilutions containing less than 1:10,000,000 gm. of protein nitrogen have accurately measureable enzymatic activity. The dry material from which these solutions were prepared was practically pure protein; hence the positive evidence indicated that the enzymes were of protein nature.

Since the positive experimental chemical, physical, biologic and immunologic evidence indicated the protein nature of the active material in pollen, we believe the protein nitrogen content of these extracts is the logical basis for their standardization. This method represents an improvement in standardization, since the nonprotein dialyzable nitrogen is inactive, and it gives a standard more closely related to the content of active substance.

We believe the assumption of the protein nature of the active material is justifiable until at least positive experimental evidence has shown the separation of active material of constant composition and free of protein.

DR. R. A. COOKE, NEW YORK, N. Y.—I suppose I should be flattered by Dr. Coca's faithful adherence to my original method of standardization of pollen extracts by the total nitrogen method. The experiments he presents today in favor of that method in preference to the recently published one of Stull and myself, based upon the protein nitrogen content of such extracts, leave much to be desired.

I could not entirely grasp the significance of the presented figures obtained by a dialysis experiment except that from them Coca concluded that the active substance was not protein. His dialysis experiments in 1925 with Grove led also to the conclusion that the active sub-

stance was not protein. Dr. Stull has discussed the technical difficulties and chemical limitations of such experiments. In addition, these experiments as reported do not take into account what should be well known regarding the difficulty with the direct skin test on account of its extraordinary delicacy. We were led into such a mistake three years ago when we first suggested that the glucoside might be one of two active substances in pollen because of the activity of the glucoside fraction in the direct test on sensitive patients. The error was obvious when we found by passive desensitization work that the protein fraction readily neutralized serum against the glucoside but that the glucoside did not readily if at all neutralize active serum against the protein.

The second series of experiments offered consists of a comparison of three timothy extracts standardized by total nitrogen. In two extracts the protein nitrogen was approximately 50 per cent of the total nitrogen, a ratio of 1 to 2; in the other it was approximately 30 per cent, or a ratio of 1 to 3. Direct skin tests with different strengths of these three extracts on a number of patients yielded, on the average, identical results. As I understand it, the argument is that the extract containing but 30 per cent of protein should have shown consistently weaker reactions if protein is the active substance. Let us examine this more carefully. A pollen extract 0.1 mg. total nitrogen contains 0.05 or 0.03 mg. protein nitrogen as the case may be if the ratio is 1 to 2 or 1 to 3. Who would venture to state that such differences could be determined by direct test? Any one even reasonably familiar with the clinical skin test would hesitate to base an argument upon results of tests with extracts so closely approximating each other.

Dr. Coca, it seems to me, has placed himself in a rather unfortunate dilemma. He argues today for the greater accuracy of standardization by total nitrogen, yet his dialysis experiments reported today as well as previously prove certainly that dialyzable nitrogen has no activity. He even believes he has proved that the so-called nondialyzable protein is not active. Then why advocate a standardization by nitrogen at all? We believe that the work of Stull, Chobot, Barnard and myself has shown that the active substance is an albuminous protein. Dr. Coca has not attempted to confirm that work by direct examination but seeks to invalidate it by experiments that are unreliable and have already been contradicted by Bouillenne and Bouillenne, Loeb and others. Dr. Coca says he is not interested in the nature of the active substance in pollen, but that does not prevent it from being a matter of interest and importance to others and a proper subject for discussion now because it is an accepted law that accurate standardization of any substance must depend upon the amount of active principle contained in it.

We believe our published work gave evidence of the protein nature of the hay fever allergen in pollen extracts. Hence, our new method of standardization by protein nitrogen, not total nitrogen, is the sounder method.

DR. M. B. SULZBERGER, NEW YORK CITY.—As I understand this discussion, it hinges mainly upon the question of whether *protein* nitrogen is the measure of the activity of a pollen extract. That, of course, is a discussion which has raged not only concerning the pollen excitant, but in anaphylaxis and allergy in general for many years.

One had to attempt to evolve and to formulate all kinds of theories when one had the protein idea in mind and attempted to explain sensitization to drugs. It never really fit here. I think you all will recall the sensitizations to different drugs, synthetic drugs which certainly contain only known chemicals and certainly no proteins. Many attempts were made to explain them on a protein sensitization basis, for instance, the theories of Bruck and of Wolff-Eisner. I think that Landsteiner probably found the solution of one important problem in his experiments with the haptens, that is, nonprotein parts of the excitants or antigens and their connection with larger molecules as carriers.

As I understand Dr. Coca's experiments and statements, he points out that, in the case of ragweed, one has succeeded, on the one hand, in getting a fraction of pollen extract which contained very little or practically no protein nitrogen and which was still decidedly active, and, on the other hand, he has a ragweed extract which contains high or, at least, quite appreciable quantities of protein nitrogen, but which is inactive. This seems to me to prove that the *protein N and excitant content do not necessarily go parallel.* However, it is quite another question to decide whether they actually do go parallel in nature. This seems to be the rule, but as Dr. Coca has shown by comparison of natural extracts, it is by no means always the case.

Dr. Coca purposely avoids the question of the nature of the pollen excitant; and rightly so—its chemical nature must be considered as unknown.

However, this report and the proof of the extremely low protein content of many atopic excitant extracts which Coca, W. Jadassohn and others have been able to produce, and, more particularly, anaphylactic sensitization (proved by Dale technic and symptoms in guinea pigs), which W. Jadassohn, Schaaf and Sulzberger were able to produce *with protein-free trichophytin polysaccharid,* certainly speak rather against the protein nature of many of these excitants. At least, I see no proof anywhere that the protein in an extract is the actual excitant and not a fortuitous finding; perhaps it is an adjuvant to sensitization rather than the whole factor.

DR. ARTHUR F. COCA.—May I show that one plate again in discussion?

There are two questions being discussed on this floor, in one of which I am not personally interested, that is the nature of the pollen excitant. It is to me at present immaterial whether it is protein or not protein. I thought I made that clear when we started. Yet several of those who have discussed what I have had to say have spent most of their time in knocking down this straw man. What I want to impress upon you is that the protein unit of Stull and Cooke as a means of standardizing pollen units is erroneous and here is the evidence. It does not need any special explanation in order to get that out of this chart.

We have used twelve different patients, and we have used different concentrations of the extracts, and we have, so far as one can see at a glance, no differences. If you add up these pluses and minuses, give them a numerical value, this middle one, which has the least precipitable nitrogen, comes out the least bit stronger than one of the other two, by accident. That is no doubt due to the technical inadequacies on the quantitative side in the preparation of the extract. But practically speaking they are identical. Yet this one (1931 specimen) has only 36 or 37 per cent precipitable nitrogen and the other two had 52.

This is the part of my message today that I would like to hear discussed by those who oppose it, not the other question in which I am not at all interested. What is the true nature of the pollen excitant? It may be protein. All that we will say now and have said ever since our first publication is that the pollen excitant is not the easily digestible or dialyzable protein. That still stands.

DR. A. H. W. CAULFEILD, TORONTO, CANADA.—I am not a biochemist in any way. I am going to refer to total nitrogens and nitrogen in the protein in a very rough manner. A number of years ago we were interested and brought forth the idea, as Dr. Cooke said, that the active substance was at least linked up with different proteins. We have been able, fortunately, to start this work again. I should like to give roughly some data that we have already obtained that refer to the straw man that Dr. Coca has referred to.

Avery, some time ago, showed that carbohydrate linked up with protein made a very effective and specific antigen. The work that we did a number of years ago led us at least to believe the active substance went with the protein. If I am not mistaken, Dr. Cooke thinks it goes only with the albumin fraction. It is perfectly true our biochemical work was not sufficiently accurate, although at that time we did come to the conclusion it was linked up with different proteins, and not solely confined to the albumin. With little better technic, or

at least the biochemists tell us we have very much better technic, we are undoubtedly at the present time showing that a carbohydrate—I am talking specifically as obtained from ragweed—linked up with a protein solution seems many times stronger as judged by skin tests or biologic tests than the same percentage of nitrogen contained in a pure protein solution. That induces the idea that perhaps the straw man may not be the man to be dealt with, but we would like to know what company he keeps when he is active.

Atopy to Gum Arabic. A. D. SPIELMAN AND H. BALDWIN, NEW YORK, N. Y. (Abstract.)

A report is given of a case of atopy to gum arabic which we believe is the first one to be so proved.

The patient, a white male, aged fifty-three years, worked as a plaster molder in a candy factory. His attacks of bronchial asthma came on six months after he had started to work in this factory. In his work the patient was exposed to dust, a large percentage of which was made up of gum arabic. Skin tests to gum arabic were markedly positive. Blood was taken for passive transfer, and again positive reactions were obtained to gum arabic.

Atopy to gum arabic is of interest because of its widespread use commercially and medically. Several thousand gum arabic infusions have been given at The Mayo Clinic with only one apparently anaphylactic reaction. However, skin tests to gum arabic on this patient were negative.

An analysis of the gum arabic used in the testing showed that it contained 0.5 per cent total nitrogen and that it gave a positive biuret test. Heidelberger's *N* free substance derived from gum arabic was also used to test the patient, but negative results were obtained. This brings up the question as to which fraction of the gum arabic is the active one—carbohydrate or protein.

This report strongly points to the advisability of testing any patient who is about to receive a gum arabic infusion, with the substance first.

Blood Sedimentation Rate in Allergic Disease. A. UFFE, PHILADELPHIA, PA. (For original article, see page 379.)

Sedimentation of Red Blood Cells in Allergic Diseases. H. WESCOTT AND W. C. SPAIN, NEW YORK, N. Y. (For original article, see page 370.)

DISCUSSION

DR. JAMES H. BARNARD, NEW YORK CITY.—In viewing the literature on this subject of sedimentation rate, there seems to be a gen-

eral consensus of opinion that it is of definite value in determining or differentiating between infective and noninfective conditions. The only exception which I recall is one by Summerville and Falls in the *Journal of Obstetrics and Gynecology*. These two men reported a number of sedimentation rates on gynecological cases which they had worked up and which had been collected on the same person from one to eight times, mostly before operation. Besides many possible errors from variations in technic, they found no unfavorable results in cases operated with high counts as compared to those with low counts. The paper, read at some particular meeting of their particular branch, was discussed unfavorably by one member of the group.

It seems as though this sedimentation test may have a place of importance in our field particularly where we are up against the diagnosis of an infection as being the true cause of some allergic condition, when we may have a person who has indefinite skin tests. That is, the patient might have some slight reactions and an indefinite clinical history to substantiate these reactions. He may also have some physical findings, suggestive of infection, and possibly some x-ray evidences that there is an infective focus. It seems as though this sedimentation study would be important here. We have the fact of the eosinophile range or quantity and the leucocyte count also pointing to this, but there is frequently the discussion as to whether a patient should have operative procedure.

Another factor which Schulhof brought out and which seems to me is of some merit is this study of the rate of an index of whether it would be proper to operate upon a patient at a certain time or whether it would be better to wait and put that patient in the hospital, there to be observed for a while and see if we cannot produce a better situation under which to operate.

The trouble, it seems to me, up to the present is the difference in the technic of doing the sedimentation rate, that is, between the Linzenmeier, Westergren and Cutler methods. And using various modifications it seems natural that one will get a variation of results. It certainly would be worth while to have a committee, I should think, to investigate the various methods and see if they could determine or arrive at some fixed procedure. Then all working with the test will use the same procedure, and as a result of that, we might be able to get much more comparable results.

DR. HARRY LEE HUBER, CHICAGO, ILL.—I think it is a very good thing for the allergists to be interested in some of these new subjects that come out in the literature. As in the proteose of Oriel a good many were slow in starting any investigation until there was a lot of discussion as to whether it was of any significance.

Recently Dr. Schuloff of Chicago emphasized the slow sedimentation rates in those with allergic diseases and in their immediate families. Our work so far corroborates, on the whole, his findings, but some of our apparent normals are also slow. All typical uncomplicated pollen cases have been slow, but our cases of urticaria have been very variable as may be expected.

I have used the Linzenmeier method alone as used by Dr. Schuloff, as it gives a little better chance for a longer time reading.

As has been pointed out several times in these papers, I think we must not become too enthusiastic about this new method, but we all ought to be interested in it and have a speaking knowledge of this subject anyway.

DR. HORACE S. BALDWIN, NEW YORK CITY.—At the New York Hospital our findings with the sedimentation rate coincide in general with the present essayists. It is sometimes difficult to know whether the symptoms are on an infectious or purely atopic basis. A determination of the sedimentation rate is helpful in this regard. Where facilities are not available for sedimentation rates, the Schilling index is an aid.

DR. M. B. SULZBERGER, NEW YORK CITY.—There are two diseases in which the "allergizing" action of infection has been studied most extensively in animals, namely, in guinea pigs; one of them is fungus infections, mycosis, and the other is tuberculosis. We all know that these are prototypes of diseases which sensitize, that is, they are diseases with basic allergic mechanisms.

I refer to the work of W. Jadassohn on the sedimentation rate in these two infections of guinea pigs. These illustrated the parallelism between sedimentation rate and course of infection, rather than the parallelism between sensitization and sedimentation rate, although there still are many inexplicable forces and influences at play here.

DR. GEORGE FLAMM.—It seems to me that before we can definitely say anything radical or definite about the sedimentation rate, we must find out exactly upon what it depends. There are various opinions held as to whether it is due to the viscosity of the blood or the fibrin content of the erythrocytes or the specific gravity. I think that the differences in the results obtained are due to the fact that we are not familiar with the causation of this sedimentation rate. That may explain the variances just as well as the different types of instruments used give different results. I think we should look for an explanation of the different results in these problems to the specific gravity or the viscosity of the blood itself. These are problems which might be undertaken.

DR. A. UFFE.—I was sorry that the short time allowed for my paper did not permit me to mention whatever little there is known so far about the theory of sedimentation. However, I must say that in that respect the sedimentation test does not differ in any way, let us say, from the Wassermann test. We know the practical application of it, while the theory underlying it is not quite well understood as yet.

I am also glad that the necessity for one universally accepted method for the performing of the sedimentation test has been brought out here. An attempt is being made to do so. Two weeks ago the American Sanatorium Association accepted the Cutler method as the standard method for their investigations. Generally speaking, the Cutler method has been used in this country much more than the other methods.

I also want to point out that we must not become very enthusiastic about using the sedimentation test as a means to determine whether we are dealing with infectious or noninfectious asthma. No man who ever worked on sedimentation ever claimed that to be so. The only claims made so far are that the sedimentation rate is always fast, first, in cases of chronic infectious diseases like tuberculosis and syphilis; second, in acute suppurative infections. This does not include chronic sinusitis, with which we deal so frequently in asthma. On Chart 3, it was shown that the number of diseased sinuses was equally large in practically every group.

The main point that I want to bring out is that when we get an asthmatic patient with a very fast sedimentation rate, we must be on the lookout. If the average amount of work done in the average case does not give us the reason why the sedimentation rate is fast, it is necessary to study that particular case a little bit more in detail than an average case of allergy.